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Association of systemic immune-inflammation index and systemic inflammation response index with chronic kidney disease: observational study of 40,937 adults

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Abstract

Background Chronic kidney disease (CKD) is linked to immunity and inflammation. Systemic immune-inflammation index (SII) and systemic inflammation response index (SIRI) are novel measures for gauging an individual's systemic inflammatory activity. We aim to investigate the potential associations between them.

Methods This study encompassed a cohort of 40,937 adults from the National Health and Nutrition Examination Survey (NHANES) 1999–2018. SII and SIRI were log2-transformed before conducting regression analysis, considering that these inflammatory markers were right skewed distributed. Weighted logistic regression models assessed the association of log2-SII and log2-SIRI levels with CKD prevalence. Weighted Cox regression models were utilized to estimate the risk of death. Subgroup analyses were performed to further clarify the effects of other covariates on the associations. Sensitivity analyses were performed to assess the robustness of our results.

Results 6986 participants with CKD were recorded, and 2818 patients died during a mean follow-up time of 100 months. After adjusting for all covariates, the highest level of log2-SII increased the CKD incidence (odds ratio [OR]: 1.47, 95% confidence intervals [CI]: 1.32–1.65, $P < 0.001$), as well as log2-SIRI (OR: 1.79, 95% CI 1.60–2.01, $P < 0.001$) when compared with the lowest level reference group. The highest level of log2-SII significantly increased all-cause mortality (hazard risk [HR]: 1.29; 95% CI 1.13–1.48, $P < 0.001$), cardiovascular mortality (HR: 1.61, 95% CI 1.25–2.09, $P < 0.001$), and hypertension mortality (HR: 1.73, 95% CI 1.23–2.42, $P = 0.001$) in CKD patients. Additionally, the positive associations were also found between log2-SIRI and all cause (HR: 1.54, 95% CI 1.35–1.76, $P < 0.001$), cardiovascular (HR: 1.90, 95% CI 1.38–2.60, $P < 0.001$), and hypertension mortality (HR: 2.15, 95% CI 1.56–2.94, $P < 0.001$). Subgroup analyses unveiled variations in these effects among different populations.

Conclusion There existed a substantial association of SII and SIRI levels with CKD prevalence, as well as mortality in patients with CKD in the U.S. population.

Keywords Systemic immune-inflammation index · Systemic inflammation response index · Chronic kidney disease · Mortality · NHANES

Introduction

More than 10% of the world's population is affected by chronic kidney disease (CKD), which is one of the leading causes of death worldwide [1]. It is anticipated that by 2040, it will be the fifth most significant contributor to the decrease in life expectancy around the world, creating a primary health concern on a global scale [2]. Consequently, it is critical to thoroughly comprehend the fundamental elements related to the development and outlook of CKD to devise successful treatment plans to stop the start and advancement of CKD.

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The development of CKD is complicated, and several risk factors, including diabetes mellitus, hypertension, and excessive salt consumption, can affect its progression [3–5]. Recent research has demonstrated that immune and inflammatory elements are essential in the development of CKD, which could be linked to the stimulation of oxidative stress, changes in tissue metabolism, endothelial cell harm, and other processes [6]. The combination of inflammation and oxidative stress in CKD progression can increase reactive oxygen species (ROS) production, resulting in apoptosis of renal vascular endothelial cells and necrosis, which can cause renal damage by disrupting microcirculatory regulation and perfusion distribution within the kidney [7, 8]. Irrespective of the cause of CKD, inflammation can contribute to glomerular and tubulointerstitial lesions.

Systemic immune-inflammation index (SII) and systemic inflammation response index (SIRI) can measure an individual's systemic inflammatory activity, demonstrating the equilibrium between inflammation and immune response [9]. Previous research has shown that SII and SIRI can be employed to evaluate local inflammation and systemic immune response, and they have been extensively utilized in the prediction of numerous illnesses [9–11], thus enhancing the effectiveness of personalized treatment [12]. Despite this, there is a need for more research into the relationship between SII and SIRI and the occurrence of CKD in the general U.S. population, as well as mortality in patients with CKD.

Materials and methods

Study design and study population

We conducted two observational studies. The associations of SII and SIRI with the occurrence of CKD in the general U.S. population were assessed by a cross-sectional study, and the correlations between SII and SIRI and the predicted risk of death in patients with CKD were investigated by a prospective cohort study, respectively.

This study incorporated National Health and Nutrition Examination Survey (NHANES) data from 1999 to 2018, with an initial enrollment of 101,316 participants. Simultaneously, we employed a set of exclusion criteria, and individuals who fulfilled any of the subsequent criteria were disqualified from participating in this study: (I) those with incomplete data in the SII and SIRI calculations; (II) those with incomplete data necessary for defining CKD; (III) pregnant [13]; (IV) below the age of 20; (V) those with incomplete data on significant covariates. In the end, the study encompassed a total of 40,937 participants. The sample's screening process was shown in detail in Fig. 1.

Definition of CKD

As per the Kidney Disease Improving Global Outcomes (KDIGO) Guidelines [14], CKD was characterized by a diminished estimated glomerular filtration rate (eGFR, <60 mL/min per 1.73 m^2) or an increased albumin-creatinine ratio (ACR, ≥ 30 mg/g). The eGFR was determined using the Chronic Kidney Disease Epidemiology Collaborative (2021 CKD-EPI) equation [15], taking into account serum creatinine (S_{Cr}) (mg/dL) data obtained through the Jaffe rate method and adjusted for gender and age.

Exposure variables

Participants' data were collected between 1999 and 2018. SII was defined as (neutrophil count) * (platelet count)/(lymphocyte count). SIRI was defined as (neutrophil count) * (monocyte count)/(lymphocyte count). Wide time interval makes the error of hematology variables because of detecting instrument. We chose Mobile Examination Centers (MEC) weights to eliminate this error. The weight calculation formula for 1999–2000 and 2001–2002 was 2/10* wtmec4yr, and the weight calculation formula for 2003–2018 was 1/10* wtmec2yr. Besides, SII and SIRI were log2-transformed before conducting regression analysis, considering that these inflammatory markers were right skewed distributed [10, 16, 17] (Figure S1).

Outcome ascertainment

The objective of the cross-sectional study was to determine the occurrence of CKD. The ultimate goal of the prospective cohort study was to assess patients' CKD progress over time. The study involved participants with CKD connected to follow-up records in the National Death Index (NDI) until December 31, 2019, and matched by NHANES respondent serial number (SEQN) to ascertain their crucial condition and the length of their follow-up.

Covariates

In light of prior research concerning the prevalence and outlook of CKD [18, 19], we ultimately examined for the incorporation of pertinent potential confounding factors. Covariates included demographic information: age (years), gender (male/female), race (Mexican American/other Hispanic/non-Hispanic white/non-Hispanic black/other race), marital status (married/living with a partner/widowed/divorced/separated), health insurance (presence/absence), body mass index (BMI) measured as body weight (kilograms) divided by height squared (square meters) determined, smoking

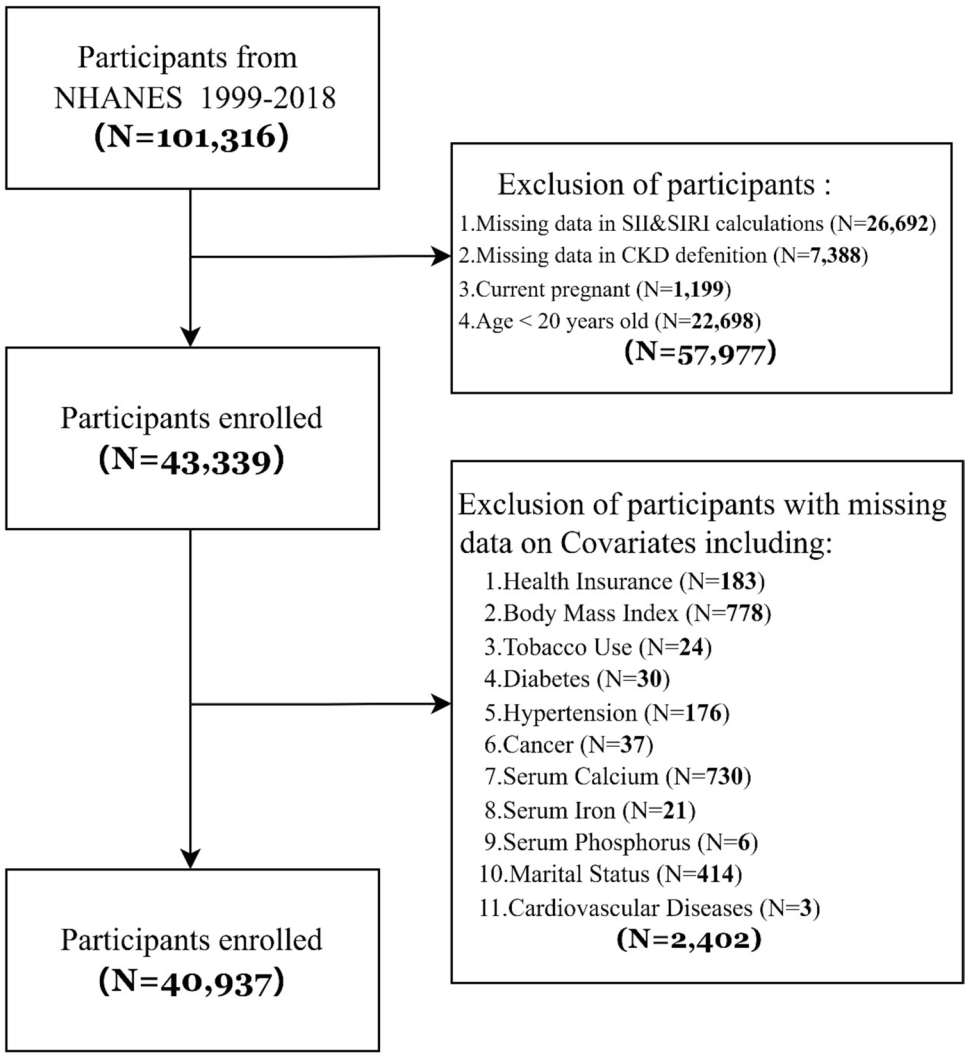

Fig. 1 Flowchart of sample selection

(yes/no, defined as smokers smoking more than 100 cigarettes in their lifetime); laboratory test data: serum calcium (mmol/L), serum iron (μmol/L), serum phosphorus (mmol/L), serum sodium (mmol/L); health information: diabetes (yes/no, defined as a diagnosis of diabetes mellitus reported by a doctor/specialist), hypertension (yes/no, expressed as a diagnosis of hypertension reported by a doctor/specialist), Cardiovascular diseases (CVD, yes/no, defined as a physician/specialist, including coronary artery disease, congestive heart failure, stroke, angina, and heart attack), cancer (yes/no, defined as a physician/specialist-reported diagnosis of cancer or malignancy).

Statistical analyses

The participants were divided into four categories according to log2-SII and log2-SIRI quaternary groupings, with the lowest levels of log2-SII and log2-SIRI acting as the benchmark. We computed the odds ratios (ORs) and 95% confidence intervals (CIs) for the effects of log2-SII and log2-SIRI on CKD morbidity and the hazard ratios (HR) and 95% confidence intervals (CIs) for the impact of log2-SII and log2-SIRI on mortality in patients with CKD for each subgroup and calculated P values before and after adjustment. We utilized the outcomes of model 3, taking into account all covariates, as the primary model. The model examined the linear trend of each subgroup's median value as a continuous variable. We used Cox proportional hazard regression models to create Kaplan–Meyer survival curves for patients, taking into account the four log2-SII and log2-SIRI subgroups.

Furthermore, we conducted distinct subgroup analyses according to the participants' initial attributes. Age (< 60, ≥ 60) and BMI (< 25, 25–30, > 30) [20] were converted to categorical variables. The interaction tests were performed across the stratified factors. This study also employed sensitivity analyses to evaluate the reliability of the results. Introducing classification for model

prediction based on quartiles, as log2-SII and log2-SIRI were continuous variables, could lead to a significant loss of information and potentially diminish the model's predictive capability. Therefore, we investigated the correlation between constant log2-SII and log2-SIRI and the mortality risk in patients with CKD by utilizing smoothed curve fitting. Logistic and Cox regression models were utilized to evaluate the correlations between log2-SII and log2-SIRI and the likelihood of CKD morbidity and mortality, respectively.

Statistical analyses were performed using the R software package (http://www.r-project.org., the R Foundation), the IBM SPSS Statistics statistical package [IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, N.Y., USA)] and Empower-Stats (http://www.empowerstats.com., X&Y Solutions, Inc., Boston, MA). Statistical significance was determined by a two-tailed test $P < 0.05$.

Results

Participant baseline characteristics

The baseline characteristics of the 40,937 participants enrolled were shown in Table 1. It was discovered that individuals with elevated log2-SII levels exhibited a higher likelihood of being older, female, non-Hispanic white, widowed/divorced, higher BMI levels, smokers, diabetes, hypertensive, cancer, higher UACR, and those with CVD. Additionally, elevated levels of log2-SII were linked to decreased serum iron, sodium concentrations, and eGFR levels. Individuals with elevated log2-SIRI levels exhibited a higher likelihood of being of advanced age, male, non-Hispanic white, widowed/divorced, possessing health insurance, higher BMI levels, smokers, diabetes, hypertensive, cancer, higher urine albumin-creatinine ratio (UACR), and those with CVD. Additionally, elevated levels of log2-SIRI were linked to decreased levels of serum iron, sodium, and phosphorus concentrations, as well as eGFR.

Association of log2-SII, log2-SIRI, and CKD prevalence risk

Table 2 displayed the outcomes of the logistic regression analyses. After adjusting for all covariates, it was observed that the likelihood of CKD prevalence rose proportionally with the escalation of log2-SII levels ($OR_{Quartile4} = 1.47$; 95% CI 1.32–1.65), and all subgroups with elevated concentrations displayed an elevated risk of CKD prevalence ($P_{trend} < 0.001$). The likelihood of CKD prevalence rose as log2-SIRI levels increased ($OR_{Quartile4} = 1.79$; 95% CI 1.60–2.01), and all subgroups of higher concentrations exhibited a higher risk of CKD prevalence ($P_{trend} < 0.001$).

Subgroup analyses and interaction tests

Table S1 displayed the outcomes of the stratified and interaction analyses based on age, gender, BMI, smoking status, diabetes, hypertension, cancer, and CVD. The interaction test revealed a noteworthy correlation between log2-SIRI and CKD in the subgroups divided by age, tobacco use, hypertension and CVD (P for interaction < 0.05), and the impact of increased log2-SIRI on the likelihood of developing CKD was more pronounced in elderly, smokers, hypertensive patients and cardiovascular patients. There was also a noteworthy correlation between smoking for log2-SII and CKD (P for interaction < 0.05), with the effect of increased log2-SII on the likelihood of developing CKD being more pronounced in smokers (Figure S2). No significant correlation was demonstrated in other strata (P for interaction tests were all > 0.05).

Baseline characteristics of patients with CKD

The baseline characteristics of the 6986 patients with CKD were summarized in Table S2 and Table S3, which were based on the four subgroup levels of log2-SII and log2-SIRI. Individuals with elevated log2-SII levels exhibited a higher likelihood of being female, non-Hispanic white, widowed, having lower serum iron and serum sodium concentrations, smoking, cancer, and a higher UACR. Individuals with elevated log2-SIRI levels exhibited a higher likelihood of being elderly, male, non-Hispanic white, widowed, possessing health insurance, having lower serum iron and serum sodium concentrations, and displaying reduced eGFR.

Association of log2-SII, log2-SIRI, and mortality in patients with CKD

The Kaplan–Meier survival curves for all-cause, CVD, and hypertension mortality in patients with CKD based on the 4 groupings of log2-SII and log2-SIRI were shown in Fig. 2. The curves all showed that participants in the Q4 group had a worse prognosis during the follow-up period (P-values for log-rank test < 0.05). Overall, these findings suggested that higher levels of log2-SII and log2-SIRI tended to have worse prognosis.

Cox regression models with stepwise adjustment for covariates were used to explore the effects of log2-SII and log2-SIRI levels in all cause mortality, cardiovascular mortality, hypertension mortality, respectively (Table 3). After adjusting for all confounders, the highest level of log2-SII significantly increased all-cause mortality (HR: 1.29; 95% CI 1.13–1.48, $P < 0.001$), cardiovascular mortality (HR:

Table 1 Baseline characteristics of quantiles of log2-SII and log2-SIRI among 40,937 participants enrolled in this study (NHANES 1999–2018)

Variables	Log2-SII					log2-SIRI				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P-value	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P-value
	< 8.479	8.479–8.940	8.940–9.421	> 9.421		< −0.448	−0.448–0.070	0.070–0.600	> 0.600	
Age (mean ± SD),years	46 ± 17	46 ± 16	46 ± 17	47 ± 17	< 0.001	44 ± 15	45 ± 16	46 ± 17	49 ± 18	< 0.001
Gender (%)					< 0.001					< 0.001
Female	5183 (45%)	4933 (50%)	5132 (52%)	5460 (58%)		6578 (59%)	5216 (53%)	4703 (49%)	4211 (44%)	
Male	6170 (55%)	4971 (50%)	4738 (48%)	4350 (42%)		4807 (41%)	4627 (47%)	5032 (51%)	5763 (56%)	
Race (%)					< 0.001					< 0.001
Mexican American	1760 (8.3%)	1757 (7.9%)	1881 (8.5%)	1694 (7.4%)		1913 (8.9%)	1875 (8.4%)	1828 (8.1%)	1476 (6.7%)	
Other Hispanic	876 (5.5%)	804 (5.5%)	787 (5.6%)	700 (5.2%)		883 (5.7%)	826 (5.8%)	774 (5.4%)	684 (4.9%)	
Non-Hispanic White	3984 (61%)	4611 (71%)	4915 (72%)	5373 (75%)		3451 (57%)	4465 (70%)	5050 (74%)	5917 (77%)	
Non-Hispanic Black	3588 (18%)	1840 (9.4%)	1531 (7.9%)	1339 (6.9%)		3883 (20%)	1826 (9.3%)	1345 (6.8%)	1244 (6.0%)	
Others	1145 (7.7%)	892 (6.4%)	756 (6.2%)	704 (5.7%)		1255 (8.9%)	851 (6.4%)	738 (5.6%)	653 (5.1%)	
Marital status (%)					< 0.001					< 0.001
Married	6024 (57%)	5485 (60%)	5325 (58%)	5001 (54%)		5986 (57%)	5381 (59%)	5325 (58%)	5143 (54%)	
Widowed	868 (5.0%)	790 (5.2%)	853 (6.1%)	1026 (7.4%)		770 (4.5%)	742 (4.9%)	836 (5.8%)	1189 (8.6%)	
Divorced	1136 (9.3%)	1001 (9.4%)	1031 (10%)	1108 (12%)		1160 (9.7%)	1013 (9.6%)	1023 (10%)	1080 (11%)	
Separated	365 (2.2%)	337 (2.4%)	314 (2.4%)	359 (3.0%)		414 (2.5%)	328 (2.3%)	306 (2.5%)	327 (2.7%)	
Never married	2062 (18%)	1578 (16%)	1665 (17%)	1691 (18%)		2173 (19%)	1616 (16%)	1593 (17%)	1614 (17%)	
Living with partner	898 (8.2%)	713 (7.2%)	682 (6.7%)	625 (6.8%)		882 (8.0%)	763 (7.6%)	652 (6.7%)	621 (6.6%)	
Health insurance (%)					0.600					0.003
Yes	8891 (81%)	7799 (82%)	7683 (82%)	7802 (82%)		8852 (81%)	7597 (82%)	7591 (81%)	8135 (83%)	
No	2462 (19%)	2105 (18%)	2187 (18%)	2008 (18%)		2533 (19%)	2246 (18%)	2144 (19%)	1839 (17%)	
Body Mass Index (mean ± SD), kg/m^2	27 ± 6	27 ± 6	28 ± 7	28 ± 8	< 0.001	27 ± 6	27 ± 6	28 ± 7	28 ± 7	< 0.001
Calcium (mean ± SD), mmol/L	2.35 ± 0.09	2.35 ± 0.09	2.35 ± 0.09	2.35 ± 0.10	< 0.001	2.35 ± 0.09	2.35 ± 0.09	2.35 ± 0.09	2.35 ± 0.10	0.011
Iron (mean ± SD), μmol/L	16 ± 6	15 ± 6	15 ± 6	14 ± 7	< 0.001	15 ± 6	15 ± 6	15 ± 6	14 ± 7	< 0.001
Sodium (mean ± SD), mmol/L	140.00 ± 2.32	139.61 ± 2.26	139.00 ± 2.36	139.00 ± 2.51	< 0.001	139.70 ± 2.29	139.00 ± 2.26	139.00 ± 2.31	139.00 ± 2.61	< 0.001
Phosphorus (mean ± SD), mmol/L	1.20 ± 0.18	1.20 ± 0.18	1.20 ± 0.18	1.20 ± 0.19	< 0.001	1.20 ± 0.17	1.20 ± 0.18	1.20 ± 0.18	1.19 ± 0.19	< 0.001
Tobacco use (%)					< 0.001					< 0.001
Yes	4968 (44%)	4441 (45%)	4652 (47%)	4934 (51%)		4502 (40%)	4316 (44%)	4682 (47%)	5495 (55%)	
No	6385 (56%)	5463 (55%)	5218 (53%)	4876 (49%)		6883 (60%)	5527 (56%)	5053 (53%)	4479 (45%)	
Diabetes (%)					< 0.001					< 0.001
No	9779 (90%)	8605 (90%)	8565 (90%)	8311 (88%)		10,039 (92%)	8643 (92%)	8349 (89%)	8229 (86%)	
Yes	1315 (8.0%)	1098 (7.7%)	1107 (8.4%)	1313 (9.8%)		1120 (6.7%)	1006 (6.8%)	1183 (8.8%)	1524 (12%)	
Borderline	259 (1.9%)	201 (1.8%)	198 (1.7%)	186 (1.8%)		226 (1.7%)	194 (1.6%)	203 (1.9%)	221 (2.1%)	
Hypertension (%)					< 0.001					< 0.001

Table 1 (continued)

Variables	Log2-SII					log2-SIRI				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P-value	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P-value
	< 8.479	8.479–8.940	8.940–9.421	> 9.421		< − 0.448	− 0.448–0.070	0.070–0.600	> 0.600	
Yes	3818 (28%)	3276 (28%)	3415 (31%)	3749 (34%)		3472 (25%)	3079 (27%)	3475 (31%)	4232 (38%)	
No	7535 (72%)	6628 (72%)	6395 (69%)	6061 (66%)		7913 (75%)	6764 (73%)	6260 (69%)	5742 (62%)	
Cancer (%)										
Yes	892 (8.5%)	822 (8.7%)	889 (8.8%)	1147 (11%)	< 0.001	743 (7.3%)	758 (8.1%)	909 (9.1%)	1340 (12%)	< 0.001
No	10,461 (91.5%)	9082 (91.3%)	8921 (91.2%)	8663 (89%)		10,642 (92.7%)	9085 (91.9%)	8826 (90.9%)	8634 (88%)	
CVD (%)					< 0.001					< 0.001
Yes	1170 (8.4%)	960 (7.5%)	1082 (8.3%)	1321 (10%)		812 (5.7%)	821 (6.3%)	1138 (9.0%)	1762 (13%)	
No	10,183 (91.6%)	8944 (92.5%)	8728 (91.7%)	8489 (90%)		10,573 (94.3%)	9022 (93.7%)	8597 (91.0%)	8212 (87.0%)	
eGFR (mean ± SD), mL/min per 1.73 m^2	99 ± 21	99 ± 20	99 ± 21	98 ± 22	0.023	100 ± 19	99 ± 20	98 ± 21	96 ± 24	< 0.001
UACR (median [IQR]), mg/g	6 [4, 10]	6 [4, 10]	6 [4, 11]	7 [5, 14]	< 0.001	6 [4, 10]	6 [4, 10]	6 [4, 11]	7 [4, 15]	< 0.001
CKD (%)					< 0.001					< 0.001
Yes	1705 (11%)	1520 (11%)	1620 (12%)	2149 (17%)		1455 (9.3%)	1370 (11%)	1632 (12%)	2537 (19%)	
No	9648 (89%)	8384 (89%)	8190 (88%)	7661 (83%)		9930 (90.7%)	8463 (89%)	8103 (88%)	7437 (81%)	

Continuous variables with skewed and normal distributions were described by median (quartiles) and mean ± standard deviation, respectively. Categorical variables were expressed as frequencies or percentages. For other normally distributed continuous variables included in the study, t-tests or analysis of variance (ANOVA) were used for comparison. For non-normally distributed continuous variables, non-parametric tests were used for comparison. The chi-square test or Fisher's exact test was used for categorical variables

Table 2 Odds ratio (95% CIs) for CKD morbidity associated with log2-SII and log2-SIRI

Independent variables	Odds ratio (95% CIs)					
	Model I	P	Model II	P	Model III	P
SII						
log2-SII	1.31 (1.25–1.38)	< 0.001	1.25 (1.19–1.31)	< 0.001	1.24 (1.18–1.31)	< 0.001
Quartiles						
Quartile 1	(Reference)		(Reference)		(Reference)	
Quartile 2	1.02 (0.91–1.13)	0.800	1.07 (0.95–1.20)	0.300	1.08 (0.96–1.22)	0.200
Quartile 3	1.10 (1.00–1.21)	0.049	1.10 (0.99–1.23)	0.068	1.10 (0.99–1.23)	0.078
Quartile 4	1.60 (1.45–1.76)	< 0.001	1.48 (1.32–1.65)	< 0.001	1.47 (1.32–1.65)	< 0.001
P for trend ψ		< 0.001		< 0.001		< 0.001
SIRI						
log2-SIRI	1.52 (1.46–1.58)	< 0.001	1.37 (1.31–1.43)	< 0.001	1.32 (1.26–1.39)	< 0.001
Quartiles						
Quartile 1	(Reference)		(Reference)		(Reference)	
Quartile 2	1.15 (1.04–1.28)	0.009	1.17 (1.04–1.32)	0.008	1.18 (1.05–1.33)	0.006
Quartile 3	1.32 (1.18–1.46)	< 0.001	1.23 (1.09–1.39)	< 0.001	1.19 (1.05–1.34)	0.006
Quartile 4	2.35 (2.15–2.57)	< 0.001	1.91 (1.71–2.14)	< 0.001	1.79 (1.60–2.01)	< 0.001
P for trend ψ		< 0.001		< 0.001		< 0.001

Model I is a univariate analysis; Model II adjusted for demographic information (gender, age, race, marital status, health insurance, BMI, tobacco use) and laboratory test data(serum calcium, serum iron, serum sodium and serum phosphorus); Model III further adjusted for health information(diabetes, hypertension, cancer, cardiovascular diseases); ψ Tests for linear trend were performed by entering the median value of each quartile as a continuous variable in the models

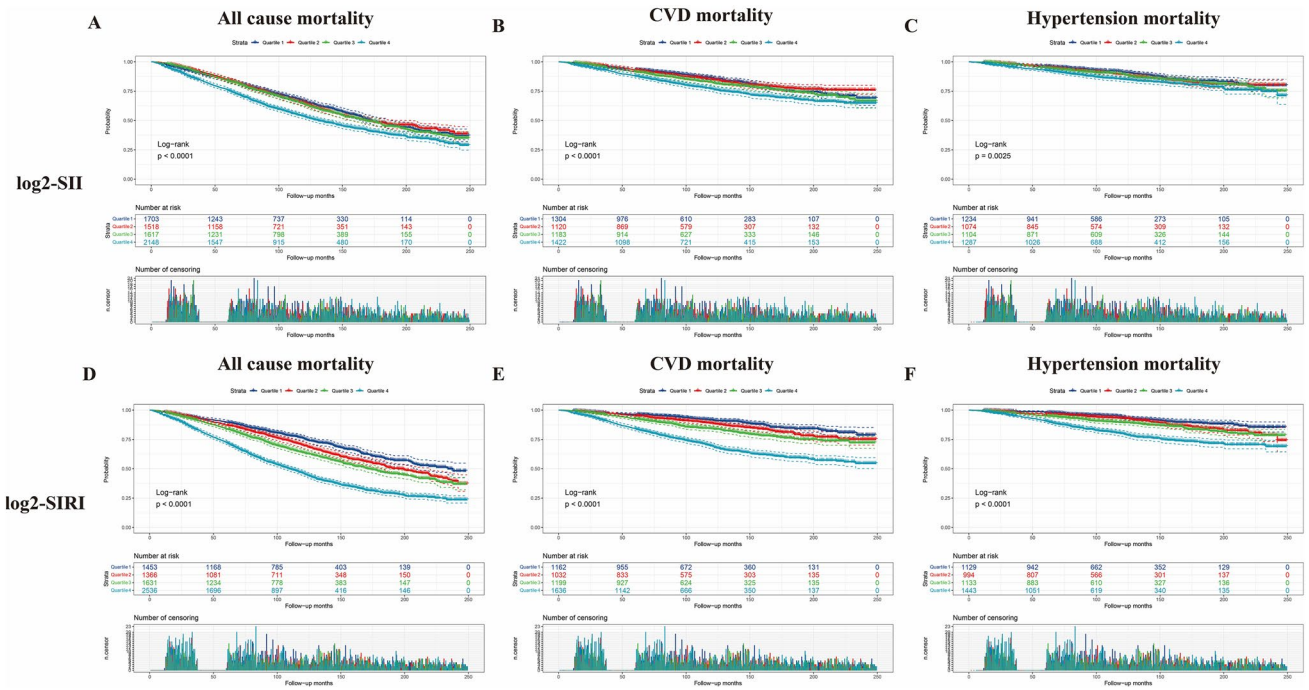

Fig. 2 Kaplan–Meier survival curves were based on the Cox proportional hazard regression models, and took into account the four log2-SII and log2-SIRI subgroups

Table 3 Hazard ratios (95% CIs) for mortality associated with log2-SII and log2-SIRI in participants with CKD

	Hazard ratios (95% CIs)					
	Model I	P	Model II	P	Model III	P
All-cause mortality						
log2-SII	1.23 (1.14–1.32)	< 0.001	1.19 (1.12–1.27)	< 0.001	1.19 (1.12–1.27)	< 0.001
Quartiles						
Quartile 1	(Reference)		(Reference)		(Reference)	
Quartile 2	0.95 (0.82–1.10)	0.500	0.98 (0.85–1.12)	0.700	0.99 (0.85–1.15)	0.900
Quartile 3	0.96 (0.83–1.11)	0.600	0.95 (0.83–1.09)	0.500	0.96 (0.83–1.10)	0.500
Quartile 4	1.34 (1.18–1.52)	< 0.001	1.28 (1.13–1.46)	< 0.001	1.29 (1.13–1.48)	< 0.001
P for trend ψ		< 0.001		< 0.001		< 0.001
CVD mortality						
log2-SII	1.42 (1.23–1.63)	< 0.001	1.39 (1.22–1.58)	< 0.001	1.38 (1.20–1.58)	< 0.001
Quartiles						
Quartile 1	(Reference)		(Reference)		(Reference)	
Quartile 2	0.93 (0.74–1.17)	0.500	1.00 (0.79–1.25)	0.900	1.03 (0.83–1.29)	0.800
Quartile 3	1.01 (0.77–1.32)	0.900	1.06 (0.79–1.41)	0.700	1.09 (0.80–1.49)	0.600
Quartile 4	1.51 (1.19–1.92)	< 0.001	1.54 (1.20–1.98)	< 0.001	1.61 (1.25–2.09)	< 0.001
P for trend ψ		< 0.001		< 0.001		< 0.001
Hypertension mortality						
log2-SII	1.31 (1.15–1.50)	< 0.001	1.39 (1.22–1.58)	< 0.001	1.37 (1.19–1.57)	< 0.001
Quartiles						
Quartile 1	(Reference)		(Reference)		(Reference)	
Quartile 2	1.13 (0.84–1.53)	0.400	1.27 (0.91–1.77)	0.200	1.32 (0.94–1.84)	0.110
Quartile 3	1.25 (0.91–1.71)	0.200	1.40 (1.02–1.94)	0.038	1.39 (1.00–1.94)	0.052
Quartile 4	1.41 (1.05–1.90)	0.024	1.76 (1.26–2.46)	< 0.001	1.73 (1.23–2.42)	0.001
P for trend ψ		0.016		< 0.001		< 0.001
All-cause mortality						
log2-SIRI	1.60 (1.50–1.70)	< 0.001	1.31 (1.24–1.38)	< 0.001	1.28 (1.22–1.35)	< 0.001
Quartiles						
Quartile 1	(Reference)		(Reference)		(Reference)	
Quartile 2	1.29 (1.06–1.57)	0.010	1.10 (0.93–1.29)	0.300	1.07 (0.90–1.26)	0.400
Quartile 3	1.57 (1.34–1.85)	< 0.001	1.18 (1.02–1.37)	0.030	1.13 (0.97–1.31)	0.110
Quartile 4	2.61 (2.24–3.05)	< 0.001	1.63 (1.42–1.86)	< 0.001	1.54 (1.35–1.76)	< 0.001
P for trend ψ		< 0.001		< 0.001		< 0.001
CVD mortality						
log2-SIRI	1.89 (1.69–2.12)	< 0.001	1.52 (1.35–1.71)	< 0.001	1.48 (1.31–1.67)	< 0.001
Quartiles						
Quartile 1	(Reference)		(Reference)		(Reference)	
Quartile 2	1.30 (0.93–1.81)	0.120	1.17 (0.88–1.55)	0.300	1.07 (0.80–1.44)	0.600
Quartile 3	1.79 (1.34–2.39)	< 0.001	1.28 (0.95–1.72)	0.110	1.20 (0.89–1.63)	0.200
Quartile 4	3.47 (2.57–4.67)	< 0.001	2.06 (1.52–2.78)	< 0.001	1.90 (1.38–2.60)	< 0.001
P for trend ψ		< 0.001		< 0.001		< 0.001
Hypertension mortality						
log2-SIRI	1.78 (1.59–1.99)	< 0.001	1.54 (1.35–1.75)	< 0.001	1.49 (1.31–1.70)	< 0.001
Quartiles						
Quartile 1	(Reference)		(Reference)		(Reference)	
Quartile 2	1.55 (1.04–2.31)	0.031	1.39 (0.97–1.98)	0.069	1.32 (0.93–1.87)	0.120
Quartile 3	1.99 (1.36–2.92)	< 0.001	1.64 (1.14–2.35)	0.008	1.57 (1.09–2.26)	0.016
Quartile 4	3.28 (2.38–4.52)	< 0.001	2.38 (1.73–3.26)	< 0.001	2.15 (1.56–2.94)	< 0.001
P for trend ψ		< 0.001		< 0.001		< 0.001

Model I is a univariate analysis; Model II adjusted for demographic information (gender, age, race, marital status, health insurance, BMI, tobacco use) and laboratory test data(serum calcium, serum iron, serum sodium and serum phosphorus); Model III Further adjusted for health information(diabetes, hypertension, cancer, cardiovascular diseases); ψ tests for linear trend were performed by entering the median value of each quartile of independent variable as a continuous variable in the models

1.61, 95% CI 1.25–2.09, P < 0.001), and hypertension mortality (HR: 1.73, 95% CI 1.23–2.42, P = 0.001) in CKD patients. Additionally, the positive associations were also found between log2-SIRI and all cause (HR: 1.54, 95% CI 1.35–1.76, P < 0.001), cardiovascular (HR: 1.90, 95% CI 1.38–2.60, P < 0.001), and hypertension mortality (HR: 2.15, 95% CI 1.56–2.94, P < 0.001).

Subgroup analyses and interaction tests

The results of stratified and interaction analyses were shown in Table 4. The results of the interaction test showed that elevated log2-SII level was more significant for increasing the risk of all-cause mortality among those obese (BMI > 30), smoked, and those with cancer. For CVD mortality, the effect of elevated log2-SII levels was more pronounced among those obese (BMI > 30). For hypertension mortality, elevated log2-SII level was more significant for increasing the risk of death in smokers. For all-cause mortality, elevated log2-SIRI level was more significant in increasing the risk of all cause and CVD mortality in obese individuals. For hypertension mortality, the effect of elevated log2-SIRI levels was more significant among smokers (P for interaction < 0.05) (Figure S3).

Sensitivity analysis

Smooth curves were shown in Figures S4 and S5. The results showed that log2-SII and log2-SIRI levels positively correlated with CKD incidence. Within a specific range, higher log2-SII and log2-SIRI levels tended to have higher all-cause mortality, CVD mortality, and hypertension mortality. Sensitivity analyses demonstrated the robustness of the findings, i.e., significant positive association of SII and SIRI levels with CKD prevalence, as well as mortality in patients with CKD in the U.S. population (Tables 2, 3).

Discussion

The present study provided comprehensive epidemiologic insights into the relationship between new metrics for assessing an individual's systemic inflammatory activity on the impact of CKD progression and prognostic outcomes. Our findings suggested that elevated levels of SII and SIRI were significantly associated with CKD prevalence, as well as mortality in patients with CKD in the U.S. population.

As indicators for assessing an individual's systemic inflammatory activity, the higher the values of SII and SIRI, the more active the body's immune system and inflammatory state [9]. A study showed that high levels of SII increased all-cause and cardiovascular mortality in patients with CKD, with more than half of the deaths in patients attributed to cardiovascular diseases [21]. The authors suggest that a possible explanation is that inflammation accelerates the progression of atherosclerosis in patients with CKD, leading to coronary artery damage, which exacerbates myocardial ischemia and strikes a blow to patients' cardiac function, ultimately leading to death.

Despite the lack of systematic studies on the association of SII and SIRI with CKD, several previous studies have demonstrated that inflammation and inflammatory responses can contribute to the progression of CKD by altering or interfering with intrarenal microcirculatory regulation and perfusion distribution, causing renal damage [22–24]. Inflammatory cells such as monocytes, neutrophils, lymphocytes, and inflammatory cytokines such as interleukin-1 (IL-1) and tumor necrosis factor-a (TNF-a) are involved in the progression of CKD by a variety of mechanisms, including an increase in pro-inflammatory cytokines, activation of oxidative stress, chronic and recurrent infections, altered adipose tissue metabolism, and dysregulation of the gut microbiota and many other mechanisms [25]. Previous studies have shown that monocytes play an essential role in the progression of CKD and that NLRP3 inflammasomes associated with renal disease when stimulated by substances such as reactive oxygen species (ROS), promote the release of IL-1 from monocytes, which in turn activates the classical pro-inflammatory signaling pathways of the intrinsic immune system, NF-kB (nuclear factor-kB) and AP-1 (activator protein-1), destroying renal units and leading to intrarenal microcirculatory dysregulation [22, 26]. In addition, neutrophils contribute to the progression of CKD through migration, production of ROS, secretion of neutrophil serine proteases (NSPs), and release of neutrophil extracellular traps (NETs) [26, 27]. Patients with CKD also experience premature aging of their T lymphocytes, which express high levels of pro-inflammatory cytokines that interact with the chronic inflammatory milieu of the patients with CKD, exacerbating the progression of the CKD and increasing the patient's susceptibility to atherosclerosis and ischemic organ damage [28–30]. In addition, the decrease in lymphocyte count also reflects patients' impaired immune resistance, making them more prone to infections and deterioration of renal function [25]. It has been demonstrated in animal studies that T lymphocytes infiltrating the kidneys increase free radicals to participate in the development of CKD and hypertension [31]. This finding is supported by observational studies showing that higher monocytes, neutrophils, and low lymphocytes are associated with a higher risk of CKD [32]. Meanwhile, platelets are involved in thrombus formation at the site of vascular injury, and changes in the PLT index reflect the severity of endothelial injury in renal vessels to some extent [33].

We found that high BMI increased all cause mortality and cardiovascular mortality in patients. This may be

Table 4 Subgroup analysis of the effect of log2-SII and log2-SIRI on the mortality among patients with chronic kidney disease

Subgroups	All cause mortality		CVD mortality		Hypertension mortality	
	HR (95% CIs)	P for interaction	HR (95% CIs)	P for interaction	HR (95% CIs)	P for interaction
Age (years)		0.282		0.380		0.393
< 60	1.32 (1.07–1.62)		1.48 (0.97–2.25)		1.20 (0.83–1.72)	
≥ 60	1.17 (1.08–1.26)		1.30 (1.11–1.51)		1.34 (1.14–1.58)	
Gender		0.511		0.118		0.800
Female	1.19 (1.09–1.30)		1.29 (1.09–1.52)		1.42 (1.16–1.73)	
Male	1.18 (1.07–1.31)		1.43 (1.17–1.77)		1.25 (0.98–1.59)	
Body mass index (kg/m^2)		**0.027**		**0.030**		0.817
< 25	1.13 (1.01–1.27)		1.10 (0.84–1.45)		1.50 (1.12–2.01)	
25–30	1.10 (0.98–1.23)		1.28 (1.02–1.61)		1.37 (1.06–1.77)	
> 30	1.32 (1.18–1.48)		1.65 (1.37–1.98)		1.22 (0.92–1.61)	
Tobacco use		**0.007**		0.059		**0.002**
Yes	1.28 (1.17–1.40)		1.54 (1.25–1.90)		1.64 (1.33–2.01)	
No	1.08 (0.97–1.20)		1.24 (1.02–1.51)		1.13 (0.93–1.38)	
Diabetes		0.351		0.510		0.220
Yes	1.20 (1.05–1.38)		1.38 (1.05–1.81)		1.44 (1.04–2.00)	
No	1.20 (1.11–1.30)		1.40 (1.17–1.68)		1.37 (1.17–1.62)	
Borderline	1.23 (0.84–1.79)		4.39 (2.89–6.67)		2.97 (1.91–3.42)	
Hypertension		0.746		0.753		0.892
Yes	1.19 (1.09–1.29)		1.34 (1.15–1.57)		1.34 (1.13–1.58)	
No	1.16 (1.02–1.33)		1.24 (0.91–1.68)		1.32 (0.91–1.93)	
Cancer		**0.049**		0.924		0.950
Yes	1.04 (0.92–1.18)		1.19 (0.89–1.60)		1.31 (0.92–1.88)	
No	1.23 (1.15–1.33)		1.34 (1.15–1.57)		1.32 (1.11–1.56)	
CVD		0.666		0.160		0.975
Yes	1.19 (1.06–1.33)		1.20 (1.00–1.45)		1.32 (1.02–1.70)	
No	1.17 (1.07–1.28)		1.48 (1.22–1.79)		1.36 (1.14–1.63)	
Age (years)		0.153		0.581		0.638
< 60	1.35 (1.15–1.58)		1.38 (0.98–1.95)		1.41 (0.98–2.04)	
≥ 60	1.32 (1.24–1.41)		1.54 (1.36–1.76)		1.63 (1.41–1.88)	
Gender		0.582		0.451		0.907
Female	1.37 (1.26–1.48)		1.54 (1.30–1.81)		1.69 (1.39–2.05)	
Male	1.29 (1.17–1.41)		1.56 (1.33–1.84)		1.53 (1.23–1.92)	
Body mass index (kg/m^2)		**0.005**		**0.042**		0.225
< 25	1.29 (1.16–1.44)		1.43 (1.08–1.89)		1.95 (1.53–2.49)	
25–30	1.20 (1.09–1.32)		1.35 (1.08–1.68)		1.51 (1.20–1.91)	
> 30	1.49 (1.35–1.65)		1.79 (1.53–2.09)		1.50 (1.17–1.93)	
Tobacco use		0.345		0.088		**0.005**
Yes	1.36 (1.26–1.47)		1.69 (1.43–2.01)		1.81 (1.52–2.16)	
No	1.29 (1.17–1.42)		1.45 (1.19–1.77)		1.40 (1.17–1.68)	
Diabetes		0.348		0.508		0.868
Yes	1.34 (1.19–1.50)		1.49 (1.22–1.84)		1.56 (1.19–2.04)	
No	1.35 (1.26–1.45)		1.61 (1.38–1.87)		1.64 (1.40–1.91)	
Borderline	1.27 (0.67–2.39)		0.35 (0.23–0.52)		1.33 (1.12–1.54)	
Hypertension		0.756		0.971		0.543
Yes	1.35 (1.25–1.45)		1.57 (1.38–1.80)		1.60 (1.36–1.87)	
No	1.28 (1.15–1.42)		1.38 (1.09–1.76)		1.74 (1.25–2.42)	
Cancer		0.063		0.689		0.521
Yes	1.21 (1.07–1.36)		1.43 (1.06–1.92)		1.65 (1.18–2.32)	
No	1.38 (1.29–1.47)		1.57 (1.37–1.81)		1.62 (1.38–1.90)	
CVD		0.391		0.931		0.364
Yes	1.39 (1.25–1.55)		1.49 (1.23–1.80)		1.66 (1.34–2.05)	
No	1.28 (1.18–1.38)		1.50 (1.28–1.76)		1.56 (1.31–1.85)	

Table 4 (continued)

Bold values represent statistically significant p-values

Subgroup analyses were performed separately for the covariates of gender, age, BMI, tobacco use, diabetes, hypertension, cancer, and cardiovascular diseases using the Cox proportional hazards regression model. The interaction tests were performed across the stratified factors

because abdominal fat deposition that may accompany obesity increases the level of inflammation and brings higher mortality in patients with CKD [34]. Our results showed that smoking interacted with SII and SIRI and increased the risk of CKD morbidity and mortality. It may be because smoking-induced endothelial dysfunction may modulate immune and inflammatory cell responses, resulting in elevated levels of inflammation [35]. In addition, smoking negatively affects many processes closely related to the development of renal fibrosis [36].

In addition, we observed that SIRI levels were associated with the incidence of CKD in the U.S. populations with different underlying diseases, including hypertension and cardiovascular disease. In terms of the effect of hypertension on the development of CKD, it may be due to the fact that hypertension is usually accompanied by additional inflammation, with elevated biomarkers of inflammation in hypertensive patients [37]. Therefore, the increased incidence of hypertension would be more pronounced. Our subgroup analysis showed that cardiovascular disease increased the risk of developing chronic kidney disease. This may be related to impaired vascular reactivity, endothelial dysfunction and increased arterial stiffness in patients with CKD [38].

Our study has several strengths. First, this study is based on the large sample size and appropriate covariates adjustment, enhancing the reliability and representativeness of our findings. In addition, we performed sensitivity analyses to assess the robustness of our results. To the best of our knowledge, this is the first study to systematically report the association between these inflammatory indices and the incidence and prognosis of CKD.

We also note some limitations of this study. First, the blood cell-based test was performed once, and the concentrations of these blood cells may change during the follow-up period, not fully reflecting the long-term inflammatory index levels in the population. In addition, single measurements of blood cell counts may be affected by other factors, which may lead to residual confounding and require attention when interpreting results. We agree that the observational nature of this study means that causality cannot be established. Going forward, more research methods as well as large-sample, multicenter cohort studies involving a larger number of participants are needed to examine these associations to provide more detailed and reliable clinical guidance. At the same time, while this study deepened the academic understanding of chronic kidney disease, it did not provide direct guidance for clinical practice or patient management. Future research could focus on how to apply these findings to real-world settings.

Conclusion

This observational study provided valuable insights into the role of systemic inflammation and immune responses in CKD. Our findings suggested that there existed a substantial association of SII and SIRI levels with CKD prevalence, as well as mortality in patients with CKD in the U.S. population. SII and SIRI may be considered effective predictors for assessing the risk of CKD morbidity in the general U.S. population and mortality risk in the CKD population. Going forward, more research methods as well as large-sample, multicenter cohort studies involving a larger number of participants are needed to examine these associations to provide more detailed and reliable clinical guidance.

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Author contributions All authors contributed to the study conception and design. Peixian Huang: conceptualization; methodology; formal analysis; writing—original draft. Yanpei Mai: methodology; formal analysis; writing—original draft; writing—review and editing. Jun Zhao, Yushan Yi: formal analysis; writing—original draft. Yaqing Wen: data curation; writing—original draft.

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Data availability The original data used in this study are nationally representative and publicly available, and can be directly obtained through application to NHANES, which is an ongoing periodic survey of a nationally representative sample of the U.S. noninstitutionalized civilian population using a complex multistage whole-population probability sampling strategy. More details about the survey can be found on the publicly available NHANES website.

Declarations

Conflict of interest The authors declare that no relationships or activities might bias their work or be perceived as biased.

Ethical approval The survey protocol for the NHANES was approved by CDC's National Center for Health Statistics Institutional Research Ethics Review Board.

Consent for publication We confirm that the manuscript has been read and approved for publication by all of the named authors, and that there are no other persons who meet the criteria for authorship but are not listed. We also confirm that the order of authorship listed in the manuscript has been approved by all of us.

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