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ORIGINAL RESEARCH

Moderate Kidney Dysfunction Independently Increases Sudden Cardiac Arrest Risk: A Community-Based Study

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BACKGROUND: Moderate kidney dysfunction is independently associated with increased cardiovascular death. Sudden cardiac arrest (SCA) accounts for at least 25% of chronic kidney disease (CKD) death. This study aimed to evaluate the impact of moderate CKD on SCA risk.

METHODS: We conducted a case–control study within a community-based investigation of SCA in the Portland, Oregon, metropolitan area from February 1, 2002, to December 31, 2020. Analysis included individuals aged 40 to 75 years who experienced SCA (cases) and individuals with no history of SCA (controls), with creatinine levels measured before SCA/enrollment. Moderate CKD was defined by an estimated glomerular filtration rate of 30 to <60 mL/min per 1.73 m^2 (2021 Chronic Kidney Disease Epidemiology Collaboration formula). A population-based SCA study in southern California was used for validation.

RESULTS: We compared 2068 SCA cases and 852 controls (mean ages, 61.4±8.5 and 62.7±8.0 years, respectively; men: 69.9% and 67.4%, respectively). SCA cases had more moderate CKD (17.7% versus 14.7%, P<0.001) and lower estimated glomerular filtration rate (74.7 versus 80.9 mL/min per 1.73 m^2, P<0.001) than controls. Multivariable regression demonstrated that moderate CKD was an independent risk factor for SCA (odds ratio, 1.32 [95% CI, 1.02–1.71]). Each 10 mL/min per 1.73 m^2 estimated glomerular filtration rate drop to <90 increased SCA risk (odds ratio, 1.24 [95% CI, 1.18–1.31]). Similar findings were observed in the validation cohort (817 SCA and 3249 controls), where moderate CKD was associated with SCA (odds ratio, 1.54 [95% CI, 1.18–2.00]).

CONCLUSIONS: Moderate CKD is associated with an increased risk of SCA in the general population. Further research into the potential integration of moderate renal dysfunction into SCA risk stratification are warranted.

Key Words: chronic kidney failure ■ community-based study ■ risk factor ■ sudden cardiac arrest

Sudden cardiac arrest (SCA) accounts for a significant proportion of death (up to 25%) among individuals with chronic kidney disease (CKD), particularly when advanced.[1–3] Associations between moderate CKD, defined as an estimated glomerular filtration rate (eGFR) of 30 to 60 mL/min per 1.73 m^2,[4] and SCA have been described but remain controversial. Previous studies have reported that moderate CKD is associated with an increased risk of SCA in individuals with left ventricular dysfunction or coronary artery disease (CAD).[5,6] A study in the general population reported that patients with non–dialysis-dependent CKD face an elevated risk of SCA and worse outcomes after cardiac arrest, with survival rates decreasing as

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CLINICAL PERSPECTIVE

What Is New?

- Our findings indicate that even moderate renal dysfunction was independently associated with sudden cardiac arrest in 2 geographically distinct populations. A decline in estimated glomerular filtration rate from 90 mL/min per 1.73 m^2 exhibited a dose–response relationship with sudden cardiac arrest.
- Among sudden cardiac arrest cases, moderate chronic kidney disease was linked to a higher likelihood of presenting with a nonshockable rhythm at the time of the event, and lower survival rates to hospital discharge compared with those with normal or mild chronic kidney disease.

What Are the Clinical Implications?

- The findings have implications for the potential integration of moderate renal dysfunction and specifically estimated glomerular filtration rate, given its dose–response relationship, into sudden cardiac arrest clinical risk stratification.

Nonstandard Abbreviations and Acronyms

CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
ORSUDS	Oregon Sudden Unexpected Death Study
PRESTO	Prediction of Sudden Death in Multi-Ethnic Communities
SCA	Sudden Cardiac Arrest

glomerular filtration rate declines.[7] However, other evidence suggests no significant association between eGFR levels of 40 to 60 mL/min per 1.73 m^2 and SCA compared with eGFR levels >60 mL/min per 1.73 m^2.[8] Moreover, due to the small number of SCA cases in previous studies, individuals with moderate CKD have often been grouped with those with advanced CKD for analysis, resulting in a lack of sufficient investigation into moderate CKD as a distinct category.[6–8] Therefore, there is a need for studies specifically designed to evaluate the relationship between moderate CKD, as a distinct condition, and SCA, as well as to investigate the potential underlying mechanisms driving this association in this unique patient population.

Additionally, in previous studies, eGFR was commonly calculated using either the Modification of Diet in Renal Disease formula or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2009/2012 formula, both of which incorporate patient age, sex, serum creatinine levels, and race. However, these equations have been shown to yield higher eGFR values for individuals identified as Black compared with non-Black individuals with similar characteristics.[9] Inker et al proposed a new equation in 2021 for estimating GFR that excludes race as a variable.[10] This approach was subsequently endorsed by the National Kidney Foundation–American Society of Nephrology Task Force. Recent studies indicate that applying the updated CKD-EPI 2021 formula has led to a significant reclassification of patients with CKD, impacting how disease severity and progression are assessed.[11,12] Moreover, moderate CKD, classified on the basis of eGFR calculated from serum creatinine using the CKD-EPI 2012 or Modification of Diet in Renal Disease formula, has been reported to predict SCA in some studies, while other studies have found no such association, particularly in older patients or the general population.[6,7,13–15]

The primary objective of this study was to address these knowledge gaps and to evaluate how moderate CKD, assessed using the updated CKD-EPI 2021 criteria, impacts the risk of SCA at the community level. Additionally, the secondary objective was to investigate potential disparities in resuscitation outcomes across the spectrum of CKD severity in SCA cases.

METHODS

Data Availability

The data in this manuscript are from an ongoing study, and there is currently no institutional review board–approved mechanism by which these data will be deposited in a public repository. All analytical methods are included in this published article. Deidentified participant data will be made available after publication upon reasonable request to the corresponding author, following approval of a proposal and a signed data use agreement.

Study Population

Study participants were selected from the ORSUDS (Oregon Sudden Unexpected Death Study), an ongoing prospective, population-based study that enrolls individuals experiencing out-of-hospital SCA within the Portland, Oregon, metropolitan area (catchment population ≈1 million). The study methods have been detailed in prior publications.[16] Briefly, SCA cases were initially identified by certified emergency medical service (EMS) providers, including the Portland Fire Department and local ambulance services. Details such as patient demographics, specifics of the cardiac arrest event (including time, location, background, witness, and bystander), resuscitation outcomes, and comorbidities were provided in the EMS narrative and care report and were recorded in accordance with Utstein standards. Upon receiving the information on SCA subjects, a comprehensive review of each case was conducted. This review encompassed the circumstances of the event and the entire medical history, obtained through medical record reviews from EMS prehospital care reports, comprehensive medical records from regional hospital systems, death certificates from Oregon state vital statistics records, and, when available, autopsy findings from the county medical examiner's office. Subsequently, SCA cases with a likely cardiac cause were determined through an in-house adjudication process involving 3 physicians on the basis of this information. SCA was defined as a sudden, pulseless collapse due to a likely cardiac cause, occurring rapidly after symptom onset when witnessed or, if unwitnessed, within 24 hours of the subject being last seen in their usual state of health.[17] Cases with noncardiac causes, such as trauma, drowning, overdose/substance abuse, terminal illness, malignancies not in remission, extracardiac causes (eg, pulmonary embolism), and other natural causes were excluded.

Acknowledging that CAD is the most common risk factor for SCA, we designed controls for the ORSUDS study to identify additional risk factors beyond CAD. In other words, our goal was to assess the risk factors for SCA in a population with a high burden of prevalent CAD, which could be considered at moderate risk for SCA. To achieve this, we prospectively recruited controls for the ORSUDS study from the same geographic area and time period as the cases. Control subjects with CAD were intentionally oversampled to produce a similar prevalence of CAD in both cases and controls, facilitating efficient adjustment for CAD in the subsequent analysis. Additionally, control subjects with any prior history of significant ventricular arrhythmias or sudden cardiac arrest were excluded. Participants were enrolled from several sources, including individuals transported by EMS for symptoms of acute coronary ischemia, patients undergoing angiography or attending outpatient cardiology clinics at a participating hospital, and members of a regional health maintenance organization.

Study Design for Discovery Cohort

For the discovery cohort of this study, we performed a case–control study in which all cases and controls from the ORSUDS study from February 1, 2002, to December 31, 2020, were selected if they were aged 40 to 75 years with detailed medical records available and serum creatinine levels measured (before arrest for cases). The serum creatinine data were obtained by 2 physicians who reviewed medical records from all our collaborating hospitals. Each serum creatinine measurement was recorded with detailed information, including the date of the test. For subjects with multiple serum creatinine measures, the one closest and before the cardiac arrest event was selected for SCA cases. For controls, the most recently measured creatinine before study entry was chosen. We selected individuals aged 40 to 75 years for 2 reasons. First, the incidence rate of sudden cardiac death is significantly lower in individuals aged <40 years, at 1.7 to 2.9 cases per 100 000 people, compared with 36.8 to 55.4 cases per 100 000 people in those aged >40 years.[18–22] Second, more than half of the population aged >75 years has an eGFR of <60 mL/min per 1.73 m^2, with most falling into the classification of moderate CKD.[23,24] Alongside the numerous comorbidities in this population, including these subjects could potentially reduce the predictive value of moderate CKD, as it is very challenging to estimate the confounding effects accurately.

The institutional review boards of Cedars-Sinai Medical Center, Oregon Health & Science University, and all relevant hospitals/health systems have approved the study protocol.

CKD was classified on the basis of eGFR, calculated using the CKD-EPI 2021 formula and the following categories: stage 1 CKD (chart history of kidney disease, with eGFR ≥90 mL/min per 1.73 m^2), stage 2 CKD (eGFR <90 and ≥60 mL/min per 1.73 m^2), stage 3a CKD (eGFR <60 and ≥45 mL/min per 1.73 m^2), stage 3b CKD (eGFR <45 and ≥30 mL/min per 1.73 m^2), stage 4 CKD (eGFR <30 and ≥15 mL/min per 1.73 m^2), and stage 5 CKD or end-stage renal disease (eGFR <15 mL/min per 1.73 m^2).[4] Moderate CKD was defined as including both stage 3a CKD and stage 3b CKD.[4] Demographic information and comorbidities were obtained from medical records from collaborating hospitals. We also included the most recent ECG and electrolytes before arrest events for SCA cases and the latest available ECGs and electrolytes for control subjects in our analysis. The ECG data were obtained from routine ECGs with a paper speed of 25 mm/s and calibration of 10 mm/mV. Heart rate and QRS duration were obtained from machine recordings. The QT, RR interval, and T_{peak}-T_{end} intervals were manually measured by trained researchers using a digital onscreen software program (DataInf Measure; DataInf GmbH, Tübingen, Germany).

External Validation Cohort Selection

To validate our findings, we replicated the analysis using data from February 1, 2015, to February 1, 2023, from the ongoing Ventura PRESTO (Prediction of Sudden Death in Multi-Ethnic Communities) study, which covers a catchment population of ≈850 000. In this study, SCA cases were identified using methods similar to those used in the ORSUDS study. This included the same approaches to case ascertainment, adjudication, inclusion criteria, data retrieval, and SCA definitions, ensuring methodological consistency. The methodology of the PRESTO study has been described previously.[25] In brief, the study included residents of Ventura County who experienced SCA with resuscitation attempts by EMS. These cases were then adjudicated by 3 physicians using information from EMS prehospital care reports, medical records from regional hospital systems, California state vital statistics death certificates, and medical examiner reports, including autopsies when available. The control group for Ventura PRESTO were patients from a regional health system (Cedars-Sinai Medical Center Medical Network, Los Angeles, CA) (n=4251) designed to represent members of the general population who obtain regular medical care. For the validation cohort, both cases and controls were selected using the criteria: individuals aged 40 to 75 years with detailed medical records and documented serum creatinine levels. All variables included in the primary data sets were also available in the validation cohort.

Statistical Analysis

Data were presented as mean±SD for continuous variables and as counts with percentages for categorical variables. Tests for differences between continuous variables were evaluated using the independent samples *t* test, while categorical variables were analyzed using Pearson's χ^2 test. Multivariable logistic regression analysis was conducted to calculate adjusted odds ratios (ORs) for moderate kidney dysfunction as a predictor of SCA. Covariates included in the regression model were demographic factors (age, race and ethnicity, and sex) and relevant risk factors or comorbidities associated with cardiac arrest and CKD: body mass index, diabetes, hypertension, chronic obstructive pulmonary disease, liver disease, congestive heart failure (CHF), CAD, and atrial fibrillation. Nonlinear relationships between the continuous variables (age and body mass index) and the risk of SCA were assessed using logistic regression with quadratic variable. Any variable demonstrating a nonlinear relationship was transformed into a categorical variable. We also calculated the adjusted ORs for each 1 mL/min per 1.73 m^2 and 10 mL/min per 1.73 m^2 decline in individuals with eGFR ≥90 mL/min per 1.73 m^2 in discovery, validation, and pooled cohort, where the pooled cohort included all individuals from both the discovery and validation groups. Furthermore, the interaction between CKD severity and sex, age (≥65 versus <65), history of hypertension, diabetes, CAD, and CHF in predicting SCA was also tested individually using multiplicative terms in logistic regression models.

To fulfill the secondary objective of this study, we conducted a case–case analysis among SCA cases to evaluate the relationship between CKD severity and resuscitation outcomes using a multivariable logistic regression model with covariates associated with survival outcome based on existing literature including demographic factors (age, race and ethnicity, and sex), history of CAD, CHF, witnesses, cardiopulmonary resuscitation by bystander, and initial rhythm recorded.[26,27] Initial rhythm was divided into nonshockable rhythms (pulseless electrical activity and asystole) and shockable rhythms (pulseless ventricular tachycardia and ventricular fibrillation). All previous analyses were repeated for the PRESTO cohort to validate the findings.

Finally, because eGFR may vary with time, we performed a sensitivity analysis in the discovery cohort, limiting the analysis to individuals with creatinine levels measured within 90 days of the cardiac arrest event for SCA cases and within 90 days of the last physician visit for controls. Statistical significance was determined at a 2-sided *P* value threshold of <0.05. All analyses were performed using SPSS Statistics version 24 (IBM, Armonk, NY).

RESULTS

Study Overview and Baseline Characteristics of Individuals With SCA in the Discovery Cohort

From February 1, 2002, to December 31, 2020, in the ORSUDS study, 6576 SCA cases were enrolled, of which 2068 met inclusion criteria for this analysis. Additionally, 852 controls meeting the criteria were also included (Figure 1). The mean ages of SCA cases and controls were 61.4 and 62.7 years, respectively. SCA cases exhibited a higher prevalence of risk factors and comorbidities, except for CAD, compared with controls. These included chronic obstructive pulmonary disease, hypertension, diabetes, CHF, and atrial fibrillation (Table 1). Additionally, SCA cases exhibited a higher ventricular rate, QRS duration, corrected QT interval, and T_{peak}-T_{end} interval compared with controls. They also showed lower sodium and calcium concentrations and higher potassium concentrations than the controls (Table S1). Of the 2920 subjects included, 2087 had normal kidney function or mild CKD, 492 had moderate CKD, and 341 had severe CKD. Compared with those with normal kidney function or mild CKD, subjects with moderate CKD were older and had a higher prevalence of all comorbidities (see Table S2).

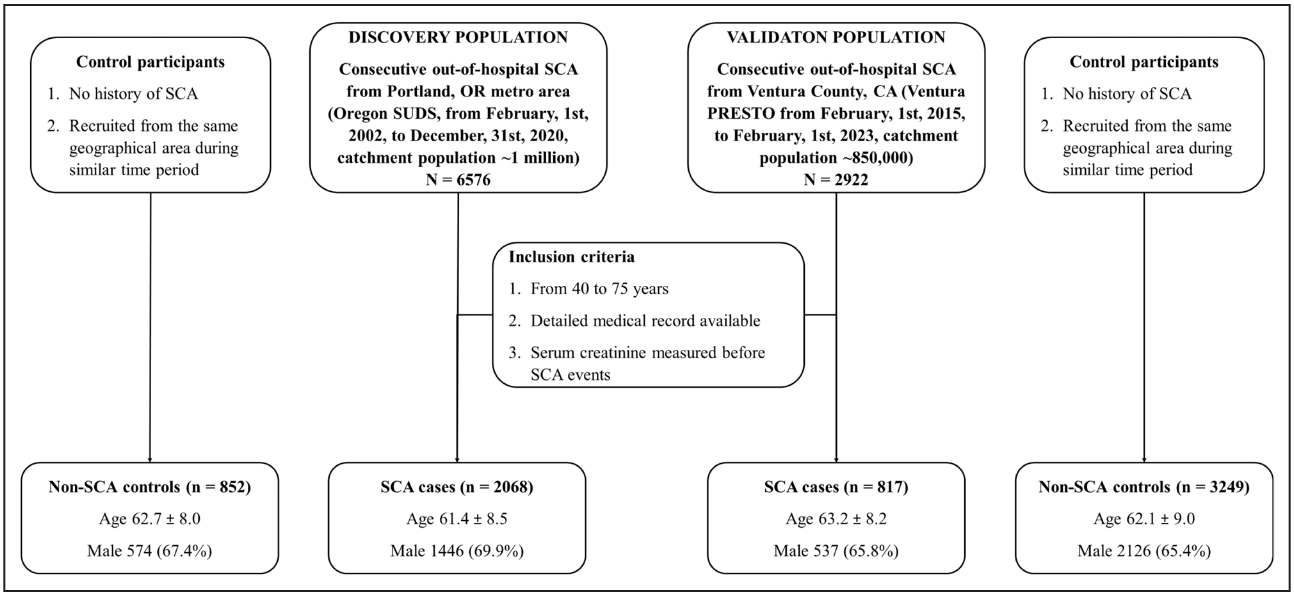

Figure 1. Flowchart of discovery and validation study population selection.
The discovery population comprised 2068 SCA cases and 852 non-SCA controls, aged 40 to 75 years, with detailed medical records and pre-SCA serum creatinine measurements from the ORSUDS study. The validation population included 817 SCA cases and 3249 non-SCA controls, aged 40 to 75 years, with detailed medical records and pre-SCA serum creatinine measurements from the PRESTO study in Ventura, California. ORSUDS indicates Oregon Sudden Unexpected Death Study; PRESTO, Prediction of Sudden Death in Multi-Ethnic Communities; and SCA, sudden cardiac arrest.

Association of Moderate CKD and SCA in the General Population

A higher proportion of SCA cases had moderate and severe CKD (stages 4 and 5) compared with controls (17.7% and 15.4% versus 14.7% and 2.6%, respectively; *P*<0.001). Additionally, SCA cases exhibited a lower median eGFR than controls (74.7 versus 80.9 mL/min per 1.73 m^2, *P*<0.001; Figure 2). Using individuals with normal kidney function (stage 1) or stage 2 CKD (eGFR ≥60 mL/min per 1.73 m^2) as the reference group, the unadjusted ORs for SCA were 1.49 (95% CI, 1.19–1.87) for moderate CKD and 7.39 (95% CI, 4.76–11.50) for severe CKD (stages 4 and 5). Our analysis revealed a nonlinear relationship between body mass index and SCA risk, leading us to convert body mass index from a continuous to a categorical variable using World Health Organization classification standards.[28] In models adjusted for demographic factors and comorbidities, CKD remained independently associated with risk of SCA with ORs of 1.32 (95% CI, 1.02–1.71) and 5.47 (95% CI, 3.50–8.79) for moderate and severe CKD (Table 2), respectively. The adjusted ORs for SCA associated with other comorbidities are also presented in Table 2. The predictive model demonstrated acceptable calibration, with the Hosmer–Lemeshow goodness-of-fit test showing χ^2 (13)=20.98 (*P*=0.07). A calibration curve is included as Figure S1. Furthermore, in study participants with an eGFR ≤90 mL/min per 1.73 m^2, each decline of 10 mL/min per 1.73 m^2 was associated with a 24% (OR, 1.24 [95% CI, 1.18–1.31]) increase in the odds of SCA, after adjusting for demographic factors and comorbidities (Figure 3). No interaction was found between moderate CKD and sex, age (≥65 years versus <65), history of hypertension, diabetes, CAD, or CHF in predicting the risk of SCA (Table S3). Finally, a sensitivity analysis was performed on participants with creatinine measured within 90 days of the cardiac arrest event for SCA cases and within 90 days of the last physician visit for controls. This analysis included 681 SCA cases and 278 controls. Moderate CKD remained independently associated with SCA, with a crude OR of 1.68 (95% CI, 1.18–2.38) and an adjusted OR of 1.54 (95% CI, 1.03–2.29).

Subgroup Analysis

Among SCA cases with initial rhythm data available (n=2026), individuals with normal or mild CKD were less likely to present with an initial rhythm of pulseless electrical activity/asystole compared with those with moderate and severe CKD (57.4% versus 68.7% and 69.2%, *P*<0.001). Moreover, they also demonstrated a trend toward higher survival-to-hospital-discharge proportion (14.8% versus 11.9% and 10.4%, *P*=0.06; Table 3). After adjusting for demographic factors (age, race and ethnicity, and sex), history of CAD and CHF, whether the event was witnessed, bystander-provided cardiopulmonary resuscitation, and the initial recorded rhythm, moderate CKD appeared as an independent predictor of lower survival to hospital discharge, with

Table 1. Baseline Characteristics of SCA Cases and Controls Aged 40–75 Years in the Discovery Cohort (ORSUDS) From the Portland, Oregon, Metro Region

	SCA cases (N=2068)	Controls (N=852)	*P* value
Age, y, mean±SD	61.4±8.5	62.7±8.0	<0.001
Male sex, n (%)	1446 (69.9)	574 (67.4)	0.18
Race and ethnicity, n (%)			0.02
White	1658 (81.0)	703 (83.6)	
Hispanic	51 (2.5)	15 (1.8)	
Asian	62 (3.0)	17 (2.0)	
Black	225 (11.0)	99 (11.8)	
Others[*]	50 (2.4)	7 (0.8)	
Missing[†]	22	11	
eGFR, mean±SD, mL/min per 1.73 m^2	69.0±31.2	78.5±21.1	<0.001
Chronic kidney disease by CKD-EPI 2021, n (%)			<0.001
Normal	618 (29.9)	272 (31.9)	
Stage 2	764 (36.9)	433 (50.8)	
Stage 3	367 (17.7)	125 (14.7)	
Stage 4	129 (6.2)	11 (1.3)	
Stage 5	190 (9.2)	11 (1.3)	
Body mass index, mean±SD, kg/m^2	32.7±10.9	30.5±7.0	<0.001
Chronic obstructive pulmonary disease, n (%)	500 (24.2)	77 (9.1)	<0.001
Hypertension, n (%)	1565 (75.8)	600 (70.7)	0.004
Liver disease, n (%)	258 (12.5)	74 (8.7)	0.004
Diabetes, n (%)	956 (46.3)	259 (30.4)	<0.001
Congestive heart failure, n (%)	757 (36.6)	108 (12.7)	<0.001
History of coronary artery disease, n (%)	976 (47.2)	456 (53.5)	0.002
Atrial fibrillation, n (%)	457 (22.1)	114 (13.4)	<0.001
Ventricular rate, beats/min, mean±SD	80.2±18.9	69.2±14.5	<0.001
Missing[†]	737	73	
QRS duration, ms, mean±SD	103.19±24.6	98.1±21.2	<0.001
Missing[†]	737	73	
T_{peak}-T_{end}, ms, mean±SD	92.0±26.5	89.9±19.2	
Missing[†]	795	74	0.04
Corrected QT interval, ms, mean±SD	468.3±44.1	439.6±39.4	<0.001
Missing[†]	773	73	

Tests for differences between continuous variables were evaluated using the independent samples *t* test, while categorical variables were analyzed using Pearson's χ^2 test. A *P* value <0.05 was considered statistically significant. CKD-EPI indicates Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; ORSUDS, Oregon Sudden Unexpected Death Study; and SCA, sudden cardiac arrest.

*Others included American Indian/Alaska Native, Native Hawaiian/Pacific Islander, and others.

†For variables with missing values, proportions and *P* values were calculated with the nonmissing data used as the denominator.

an adjusted OR of 0.60 (95% CI, 0.39–0.92; *P*=0.02; Table S4). The model fit was satisfactory, with the Hosmer–Lemeshow goodness-of-fit test yielding χ^2(8)=11.85 (*P*=0.16) for initial rhythm (ventricular tachycardia/ventricular fibrillation) prediction and χ^2(8)=8.36 (*P*=0.40) for survival prediction.

Validation Analysis

There were 817 SCA cases and 3249 controls from the PRESTO study who met the inclusion criteria, with mean ages of 63.2 and 62.1 years, respectively. As in ORSUDS, SCA cases in PRESTO had a higher prevalence of most comorbidities evaluated compared with controls. Additionally, a greater proportion of SCA cases had moderate CKD compared with controls (22.6% versus 14.9%, *P*<0.001; Table S5). Using eGFR ≥60 mL/min per 1.73 m^2 as the reference group, the crude ORs for SCA were 2.34 (95% CI, 1.92–2.85) for moderate CKD and 25.22 (95% CI, 17.94–35.45) for severe CKD. After adjusting for demographic variables and comorbidities the adjusted ORs were 1.54 (95% CI, 1.18–2.00) for moderate CKD and 9.41 (95% CI, 6.06–14.61) for severe CKD (Table 2). Moreover, a decline in eGFR from 90 mL/min per 1.73 m^2 by each 1 mL/min per 1.73 m^2 and 10 mL/min per 1.73 m^2 was

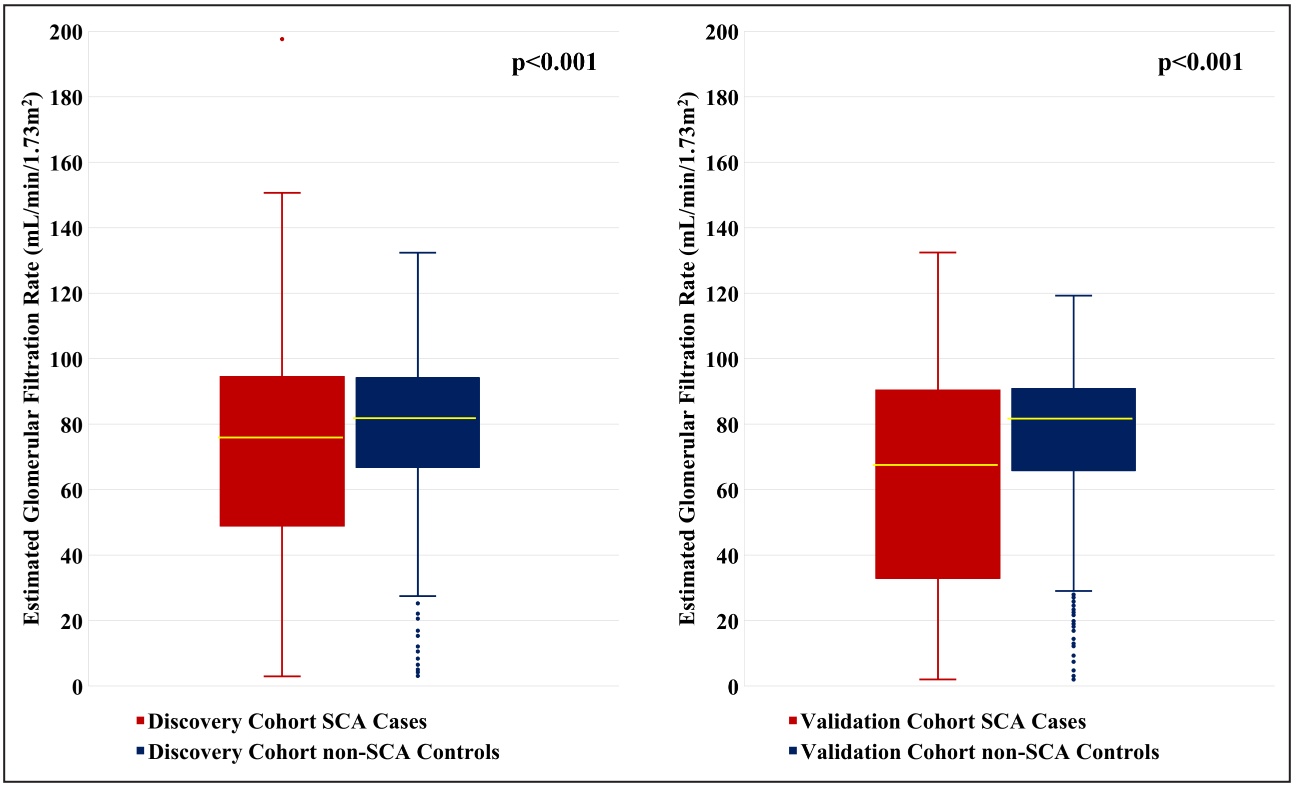

Figure 2. Estimated glomerular filtration rate of SCA cases and controls in discovery and validation cohorts.
In the discovery cohort, SCA cases had a lower median (eGFR) compared with their non-SCA control counterparts (74.7 [95% CI, 48.9–94.4] vs 80.9 [95% CI, 66.9–94.1]; *P*<0.001). A similar finding was observed in the validation cohort, where SCA cases exhibited significantly lower eGFR than controls (64.5 [95% CI, 33.0–90.3] vs 78.3 [95% CI, 65.9–90.7]; *P*<0.001). Differences were assessed using the independent samples *t* test, with a *P* value of <0.05 being considered statistically significant. eGFR indicates estimated glomerular filtration rate; and SCA, sudden cardiac arrest.

Table 2. Multivariable Adjusted Odds Ratios for sudden Cardiac Arrest by CKD Severity and Other Comorbidities in Discovery (ORSUDS) and Validation (PRESTO) Cohorts

	ORSUDS	PRESTO
CKD		
Normal or mild	Reference	Reference
Moderate	1.32 (1.02–1.71)	1.54 (1.18–2.00)
Severe	5.47 (3.40–8.79)	9.41 (6.06–14.61)
Chronic obstructive pulmonary disease	3.01 (2.28–3.98)	3.01 (2.19–4.13)
Hypertension	1.08 (0.88–1.33)	1.73 (1.35–2.22)
Liver disease	1.04 (0.77–1.42)	0.53 (0.39–0.72)
Diabetes	1.47 (1.20–1.81)	2.63 (2.11–3.28)
Congestive heart failure	3.10 (2.39–4.02)	3.97 (2.82–5.59)
Coronary artery disease	0.45 (0.37–0.54)	1.63 (1.28–2.06)
Atrial fibrillation	1.22 (0.94–1.59)	17.18 (10.44–28.26)

In the multivariable logistic regression model, odds ratios were adjusted for demographic variables (age, race and ethnicity, and sex) and relevant risk factors and comorbidities associated with cardiac arrest and CKD. These included body mass index, classified according to World Health Organization standards with the normal class as the reference, along with medical histories of diabetes, hypertension, chronic obstructive pulmonary disease, liver disease, congestive heart failure, coronary artery disease, and atrial fibrillation. CKD, chronic kidney disease; ORSUDS, Oregon Sudden Unexpected Death Study; and PRESTO, Prediction of Sudden Death in Multi-Ethnic Communities.

associated to an increased adjusted OR for SCA of 1.04 (95% CI, 1.03–1.04) and 1.41 (95% CI, 1.31–1.50), respectively.

Among SCA cases, individuals with normal renal function or mild CKD were less likely to present with an initial rhythm of pulseless electrical activity/asystole compared with those with moderate and severe CKD (76.7% versus 78.9% and 84.4%, *P*=0.09). Additionally, SCA cases with normal/mild CKD demonstrated a higher proportion of return of spontaneous circulation and survival to hospital discharge than their moderate and severe CKD counterparts (Table 3). After adjusting for demographic factors (age, race and ethnicity, and sex), history of CAD, CHF, witnessed status, bystander-performed cardiopulmonary resuscitation, and the initial rhythm recorded, moderate CKD appeared as an independent predictor of failure to survive until hospital discharge, with an adjusted OR of 3.19 (95% CI, 1.13–9.09; *P*=0.03; Table S4).

DISCUSSION

We report that moderate CKD was independently associated with SCA in our discovery cohort (ORSUDS). This association was confirmed in a sensitivity analysis

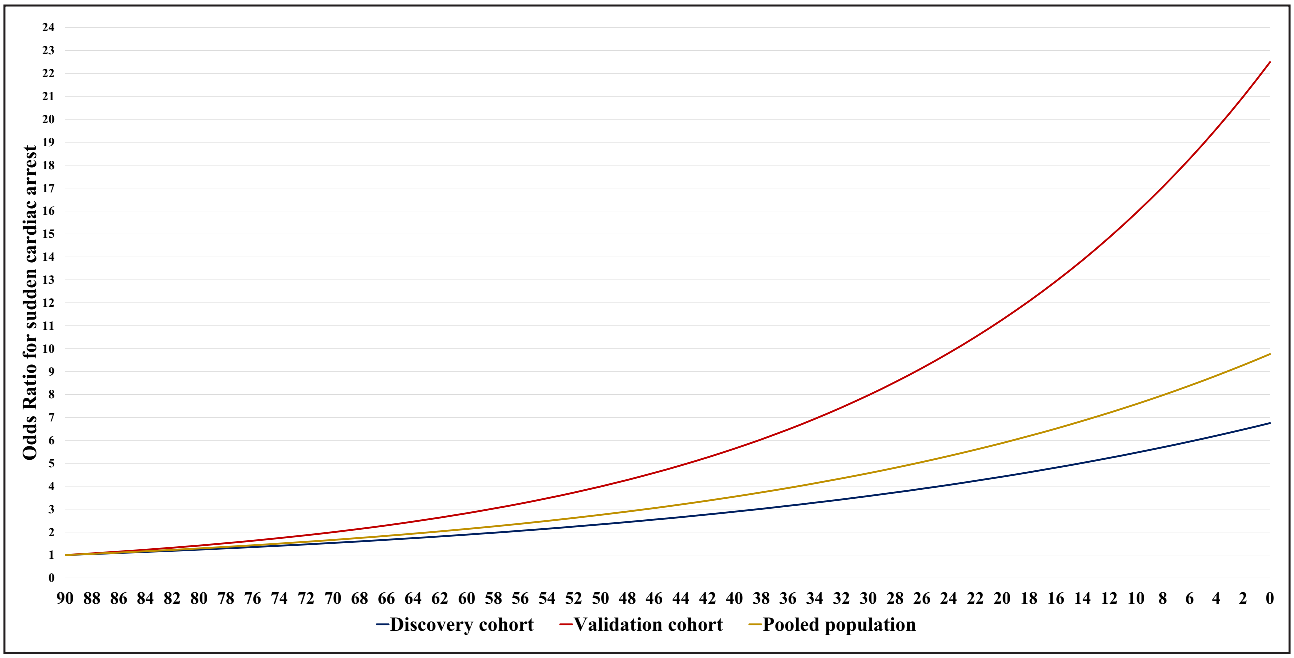

Figure 3. Odds ratio for risk of SCA by eGFR (with ≥90 mL/min per 1.73 m^2 as reference) in discovery, validation, and pooled population.

The risk of SCA increases as the eGFR decreases in both the discovery and validation cohorts, as well as in the pooled population. eGFR indicates estimated glomerular filtration rate; and SCA, sudden cardiac arrest.

Table 3. Resuscitation Characteristics of Sudden Cardiac Arrest Cases in Discovery (ORSUDS) and Validation (PRESTO) Cohorts With Different Severity of CKD

	Discovery cohort: ORSUDS				Validation cohort: PRESTO			
	Normal/mild CKD (n=1382)	Moderate CKD (n=367)	Severe CKD (n=319)	*P* value	Normal/mild CKD (n=446)	Moderate CKD (n=185)	Severe CKD (n=186)	*P* value
Location, n (%)				<0.001				<0.001
Home	866 (63.1)	237 (64.6)	170 (53.5)		358 (80.3)	148 (80.0)	128 (68.8)	
Care facilities*	165 (12.0)	66 (18.0)	115 (36.2)		38 (8.5)	24 (13.0)	54 (29.0)	
Public	301 (21.9)	54 (14.7)	28 (8.8)		46 (10.3)	12 (6.5)	4 (2.2)	
Other	40 (2.9)	10 (2.7)	5 (1.6)		4 (0.9)	1 (0.5)	0 (0.0)	
Missing†	10	0	1					
Witnessed, n (%)	792 (57.8)	215 (58.9)	180 (56.6)	0.8	191 (42.9)	80 (43.2)	71 (38.2)	0.5
Missing†	12	2	1					
Bystander CPR, n (%)	617 (44.6)	141 (38.4)	148 (46.4)	0.06	240 (53.8)	93 (50.3)	100 (53.8)	0.7
Initial presenting rhythm, n (%)				<0.001				0.09
VF/VT	577 (42.6)	111 (30.8)	98 (31.3)		104 (23.3)	39 (21.1)	29 (15.6)	
PEA/asystole	776 (57.4)	249 (69.2)	215 (68.7)		342 (76.7)	146 (78.9)	157 (84.4)	
Missing†	29	7	6					
Survival to hospital discharge, n (%)	204 (14.8)	38 (10.4)	38 (11.9)	0.06	40 (9.0)	5 (2.7)	4 (2.2)	<0.001
Missing†	1		1					

Tests for differences between continuous variables were evaluated using the independent samples *t* test, while categorical variables were analyzed using Pearson's χ^2 test. A *P* value <0.05 was considered statistically significant. A *P* value <0.05 was considered statistically significant. CKD indicates chronic kidney disease; CPR, cardiopulmonary resuscitation; ORSUDS, Oregon Sudden Unexpected Death Study; PEA, pulseless electrical activity; PRESTO, Prediction of Sudden Death in Multi-Ethnic Communities; SCA, sudden cardiac arrest; and VF/VT, ventricular fibrillation/ventricular tachycardia.

*Care facilities include nursing homes, outpatient clinics, and emergency department.

†For variables with missing values, proportions and *P* values were calculated with the nonmissing data used as the denominator.

restricted to individuals with recently measured eGFR (within 3 months). Moreover, a reduced eGFR <90 mL/min per 1.73 m^2 appeared to have a dose–response association with SCA. Among SCA cases, moderate CKD was associated with a higher likelihood of presenting with a nonshockable rhythm as the initial cardiac rhythm and lower survival rates to hospital discharge. These findings were validated in the geographically distinct PRESTO cohort.

Using 2 cohorts with distinct baseline characteristics—a younger population with a high prevalence of CAD and CHF in the discovery cohort (ORSUDS) and an older but relatively healthier population in the validation cohort (PRESTO)—we demonstrated that moderate CKD is associated with an increased risk of SCA in the general population. This observation aligns with prior studies and underscores that the association remains significant when eGFR is estimated using either serum creatinine or cystatin C and across age groups, from younger to older individuals.[5–7,13–15,29] Notably, we found that even a modest decline in eGFR from 90 mL/min per 1.73 m^2 was associated with an increased risk of SCA, ranging from 24% to 41% for every 10 mL/min per 1.73 m^2 decrease. These findings indicate a higher risk increase than previous reports, which estimated a risk increase of 11% to 17% in populations with CHF and CAD.[5,6] This discrepancy likely reflects our study focus on the general population, which typically has a lower baseline risk of SCA than those with CHF or CAD. Consequently, the relatively greater observed impact of moderate CKD on SCA risk in our study is notable. Finally, our findings indicate that moderate CKD presents a risk comparable to well-known risk factors such as diabetes (hazard ratio [HR], 2.60 [95% CI, 1.30–5.30]), hypertension (relative risk, 2.10 [95% CI, 1.71–2.58]), chronic obstructive pulmonary disease (relative risk, 1.68 [95% CI, 1.28–2.21]), and congestive heart failure (HR, 2.13 [95% CI, 1.53–2.98]).[30–33] In addition to being an independent risk factor for SCA, moderate CKD has been shown to potentially increase the mortality rate when combined with other risk factors such as diabetes, hypertension, and hyperlipidemia.[34] This highlights the importance of paying close attention to moderate CKD as a significant risk factor.

Moderate CKD can potentially contribute to SCA through multiple mechanisms, including exaggerated activity of the renin–angiotensin–aldosterone system and the sympathetic nervous system, as well as increased inflammation, fluid retention,[35] and electrolyte imbalances.[36] These factors collectively promote left ventricular hypertrophy, remodeling, fibrosis, and vasculopathy in both large (atherosclerosis) and small vessels (arteriolosclerosis), resulting in ischemic heart disease. These consequences not only lead to heart failure but also predispose to cardiac arrhythmias through reentry pathways and conduction system disruption.[36–39] Our study demonstrated that individuals with moderate CKD had higher proportion of comorbidities, including obesity, diabetes, hypertension, chronic obstructive pulmonary disease, CAD, CHF, and atrial fibrillation, compared with those with normal or mild CKD. Recognizing that moderate CKD is an independent risk factor for SCA, clinicians should consider a comprehensive approach that includes the treatment of comorbidities according to guidelines, lifestyle modifications, and the implementation of SCA prevention strategies. Pharmacological interventions such as β blockers, renin–angiotensin–aldosterone system inhibitors, and calcium channel blockers should be carefully considered and initiated even in patients with a modest decline in renal function.[35,40,41]

Additionally, regarding resuscitation characteristics, among SCA cases, moderate CKD was associated with a higher proportion of initial nonshockable rhythms. These findings are consistent with our previous, machine learning–based analysis of ventricular fibrillation versus pulseless electrical activity.[42] Also, these results align with previous studies on rhythm monitoring in patients with CKD, particularly those undergoing hemodialysis, which showed that bradycardia and asystole, rather than ventricular arrhythmias, were the most common arrhythmias in these individuals.[43–45] Patients with moderate CKD are prone to ventricular fibrosis, which alters intracardiac conduction and is associated with conduction blocks. Furthermore, they often have anemia, which limits cell energy and makes the cardiac myocytes more vulnerable to global myocardial energy depletion, contributing to nonshockable rhythms.[42,46] Moreover, SCA cases with moderate CKD had worse outcomes, with lower survival rates to hospital discharge compared with those with normal or mild CKD. This finding can be explained by the higher proportion of nonshockable rhythms, which were associated with poorer outcomes, and by the additional burden of CKD, which involves electrolyte and fluid imbalances.

Finally, considering the high mortality rate associated with SCA, moderate CKD could be an important factor in developing a risk prediction score for SCA in the general population. By using eGFR instead of categorical classifications, incorporating moderate CKD into risk stratification may enhance the accuracy of previously developed SCA risk scores.[47,48] The dynamic nature of eGFR could offer a more accurate reflection of changes in SCA risk over time. Additionally, using a race-free formula to calculate eGFR could further enhance the generalizability of the risk score across different racial groups.[49] Additionally, raising awareness among clinicians and patients about the significance of moderate kidney dysfunction could potentially enhance SCA prevention and outcomes.

Strengths and Limitations

Our study possesses several strengths worth noting. First, it is a community-based study encompassing 2 distinct populations: the ORSUDS cohort in Oregon, characterized by younger participants, a higher proportion of White individuals, and a more prominent cardiac disease burden; and the PRESTO cohort in Ventura County, which included older participants, a higher representation of Hispanic individuals, and lower cardiac disease prevalence. Despite these demographic and clinical differences, most of our findings were consistent across cohorts. Additionally, compared with other community-based studies, our work had a broader age range and racial and ethnic diversity, enhancing the generalizability of our findings.[7,14] Second, our study design integrated data from the EMS system and a strict and systematic adjudication of SCA, providing a more comprehensive assessment and robust evaluation of the burden of SCA among patients with CKD in the community compared with prior studies relying solely on *International Classification of Diseases* (*ICD*) codes for SCA definition. Finally, our analyses incorporated adjustments for various confounders previously demonstrated to be associated with CKD and SCA, strengthening the evidence for an independent association between CKD and SCA.

However, certain limitations should be acknowledged when interpreting our findings. First, the research is based on 2 large community-based observational studies. While we used multivariable regression models to reduce confounding bias, some residual confounding may persist. Second, the lack of alternative methods to estimate renal function, such as eGFR calculated using cystatin C or the urine albumin-to-creatinine ratio, limits our ability to explore other perspectives of renal function and albuminuria in relation to SCA. Finally, given the nature of out-of-hospital SCA, the initial rhythm data could be influenced by delays in EMS response, potentially underestimating the proportion of shockable rhythms and limiting our ability to characterize the true underlying rhythm at the time of arrest.

CONCLUSIONS

In conclusion, both moderate and severe CKD were associated with a significantly increased risk of SCA in the general population. Our findings underscore the importance of further research to elucidate the role of renal dysfunction in mechanisms of lethal arrhythmias and to evaluate the potential role of moderate renal dysfunction for improving SCA risk stratification.

ARTICLE INFORMATION

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Disclosures

All other authors have reported that they have no relationships to disclose that are relevant to the contents of this paper.

Supplemental Material

Tables S1–S5
Figure S1

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