ORIGINAL RESEARCH

Long-Term Risk of Cardiovascular Events in Patients With Chronic Kidney Disease Who Have Survived Sepsis: A Nationwide Cohort Study

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***Background*—**Long-term cardiovascular outcomes after sepsis in patients with chronic kidney disease are not well known. We aimed to examine the risk of subsequent cardiovascular events in patients with chronic kidney disease discharged after hospitalization for sepsis in Taiwan.

***Methods and Results*—**Using complete claims data for patients with chronic kidney disease from Taiwan's National Health Insurance Research Database, we identified patients with sepsis who survived hospitalization between 2000 and 2010. Each sepsis survivor was propensity score–matched to one nonsepsis hospitalized control patient. Cox regression models were used to estimate the hazard ratios (HRs) of clinical outcomes, including major adverse cardiovascular events (myocardial infarction and ischemic stroke), hospitalization for heart failure, and all-cause death. Among 66 961 sepsis survivors, the incidence rates of all-cause mortality and major adverse cardiovascular events during the study period were 288.51 and 47.05 per 1000 person-years, respectively. In comparison with matched hospitalized nonsepsis control patients, sepsis survivors had greater risks of major adverse cardiovascular events (HR, 1.42; 95% CI, 1.37–1.47), myocardial infarction (HR, 1.39; 95% CI, 1.32–1.47), ischemic stroke (HR, 1.46; 95% CI, 1.40–1.52), hospitalization for heart failure (HR, 1.55; 95% CI, 1.51–1.59), and all-cause mortality (HR, 1.56; 95% CI, 1.54–1.58). The results remained unchanged in analyses of several subgroups of patients, and were similar in analyses accounting for the competing risk of death.

***Conclusions*—**Our findings highlight the association of sepsis with a significantly increased long-term risk of cardiovascular events among survivors in the chronic kidney disease population. **(*J Am Heart Assoc*. 2017;6:e004613. DOI: 10.1161/JAHA.116.004613.)**

Key Words: cardiovascular events • chronic kidney disease • epidemiology • infection • sepsis

Chronic kidney disease (CKD) affects about 10% of the general adult population worldwide, and most cases are complicated by sepsis and cardiovascular disease (CVD).[1] In preclinical studies, potential biologic plausibility has shown that a sepsis-induced inflammatory cascade was responsible for adverse cardiovascular effects through endothelial dysfunction, platelet activation, or atherosclerosis progression.[2] In addition, a growing body of evidence supports the positive association between sepsis and future cardiovascular events (CVEs), which has been observed consistently in patients with numerous types of infection, ranging from respiratory or urinary tract infection[3] to pneumonia requiring hospitalization[4] and severe sepsis requiring intensive care unit (ICU) admission.[5–7] However, most studies have involved small selected populations (eg, older or community populations), the inclusion of controls with imbalanced baseline conditions, and/or lack of consideration of the competing risk of death.[5,8,9] Few studies have specifically addressed the role

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Accompanying Tables S1 through S4 are available at http://jaha.ahajournals.org/content/6/2/e004613/DC1/embed/inline-supplementary-material-1.pdf

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of sepsis in subsequent cardiovascular risk in populations of individuals with CKD, in whom sepsis remains the leading cause of hospitalization.[10]

Although studies conducted during the past decade have found a significant increase in the risk of CVEs following sepsis episodes in the dialysis population,[11–13] a knowledge gap remains for nondialysis patients with CKD. Since the long-term mortality rate of sepsis survivors remains high,[14] it cannot be fully ascribed from preexisting chronic illness before onset of infection.[5] To systematically address the impact of sepsis on further cardiovascular consequences, we designed a contemporary nationwide population-based cohort study to evaluate the long-term risk of CVD among dialysis and nondialysis patients with CKD who survived sepsis in comparison with propensity score–matched nonsepsis hospitalized controls.

Methods

Data Source

The institutional review board of Taipei City Hospital approved this study (TCHIRB-1030603-W), and the need for a full ethical review was waived because we utilized deidentified claims data exclusively from Taiwan's National Health Insurance Research Database (NHIRD), which collects information for more than 99% of Taiwan's 23 million inhabitants. This information includes patient demographics, diagnoses, procedures, and prescriptions administered at outpatient, inpatient, and emergency services. Diagnostic information is based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM). We have described this database in detail in previous studies.[15–18]

Study Cohort

We identified all patients with CKD aged ≥20 years in Taiwan between January 1, 2000, and December 31, 2011. CKD cases were defined according to the registry of ICD-9-CM code 585 at 1 or more inpatient or 2 or more outpatient visits.[19,20] The accuracy of CKD diagnoses recorded in the database has been validated with a positive predictive value of 90.4%[21] and a negative predicted values of over 90%.[22] Most patients in Taiwan with coded diagnoses of CKD are categorized as having stage 3 to 5 according to the estimated glomerular filtration rate–based definition (ie, <60 mL/min per 1.73 m^2).[21] Two cohorts were established based on the presence or absence of sepsis in CKD claims. The sepsis cohort comprised all patients with CKD who had first-time discharge diagnoses of sepsis (ICD-9-CM code 038.x) and received antibiotic treatment during hospitalization. Our previous study validated the specificity of coded diagnoses of sepsis in Taiwan's NHIRD.[16] For the control cohort, we identified CKD patients who were hospitalized with nonsepsis diagnoses. We used index discharge data to examine subsequent cardiovascular outcomes, and excluded patients in both cohorts who died during hospitalizations. The index date was defined as the first day of discharge from hospitalization.

We collected data on the following baseline covariates: (1) demographic covariates (age, sex, year of index date, month of index date, monthly income, urbanization level, hospital level, and Charlson Comorbidity Index); (2) concomitant use of medications associated with CVD (antiplatelet agents, insulin, oral antihyperglycemic drugs, diuretics, β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, statins, and steroids); and (3) relevant comorbidities, defined by ICD-9-CM codes, which are not included in the Charlson Comorbidity Index calculation (Table 1). Because of potential confounding between the sepsis and nonsepsis cohorts, we calculated a propensity score (probability of hospitalization for sepsis) for each patient in both cohorts by accounting for baseline covariates (Table S1). We matched each patient in the sepsis cohort to a control patient based on dialysis status and similarity of propensity score, which was generated by nearest-neighbor matching without replacement, using a caliper width equal to 0.1 of the SD of the logit of the propensity score.

Outcomes

The clinical outcomes of primary interest were hospitalization with the principal diagnosis of myocardial infarction (ICD-9-CM code 410.x), ischemic stroke (ICD-9-CM code 433.x, 434.x, or 436) or heart failure (ICD-9-CM code 428.x), and all-cause mortality. We also considered a composite outcome —major adverse cardiovascular events (MACEs)—that included myocardial infarction and ischemic stroke. Previous studies have shown good diagnostic accuracy for the detection of comorbidities such as ischemic stroke[22,23] and myocardial infarction[24] using ICD-9-CM codes. All patients were followed until death or December 31, 2012.

Statistical Analysis

Descriptive statistics were used to characterize baseline demographic and clinical variables of the study cohort. We used a standardized difference to check for balance between the sepsis and control cohorts after matching. We calculated the incidence rates of MACEs in the two cohorts using Poisson distribution. The log-rank test was used to assess differences in the incidence rate of CVEs following sepsis between cohorts.

Table 1. Demographic and Clinical Characteristics of the CKD Patients With Sepsis and the Nonsepsis Control Cohort

Characteristic	Before Propensity Score–Matched			Propensity Score–Matched		
	CKD Patients With Sepsis	Nonsepsis Control Cohort	Standardized Difference	CKD Patients With Sepsis	Nonsepsis Control Cohort	Standardized Difference
No. of patients	66 961	237 941		65 265	65 265	
Mean age (SD), y	71.1 (13.2)	66.4 (14.7)	0.341	71.0 (13.2)	70.9 (12.8)	0.007
Men	34 849 (52.0)	137 289 (57.7)	−0.114	34 304 (52.6)	34 420 (52.7)	−0.004
Monthly income, NT$						
Dependent	26 305 (39.3)	78 100 (32.8)	0.135	25 347 (38.8)	25 058 (38.4)	0.009
<19 100	16 072 (24.0)	56 229 (23.6)	0.009	15 762 (24.2)	15 980 (24.5)	0.000
19 100–42 000	23 630 (35.3)	94 583 (39.8)	−0.092	23 206 (35.6)	23 258 (35.6)	−0.002
>42 000	954 (1.4)	9029 (3.8)	−0.149	950 (1.5)	969 (1.5)	−0.002
Urbanization level						
1	19 481 (29.1)	74 220 (31.2)	−0.046	19 023 (29.1)	18 977 (29.1)	0.002
2	43 421 (64.8)	149 938 (63.0)	0.038	42 295 (64.8)	42 385 (64.9)	−0.003
3	3376 (5.0)	11 507 (4.8)	0.009	3283 (5.0)	3263 (5.0)	0.001
4 (rural)	683 (1.0)	2276 (1.0)	0.006	664 (1.0)	640 (1.0)	0.004
Charlson Comorbidity Index score, median (IQR)	8 (6–10)	7 (5–9)	0.440	8 (6–10)	8 (6–10)	−0.013
Concomitant medications						
Antiplatelet agent	16 111 (24.1)	69 234 (29.1)	−0.114	15 916 (24.4)	15 952 (24.4)	−0.001
Insulin	8146 (12.2)	18 216 (7.7)	0.151	7563 (11.6)	7723 (11.8)	−0.008
Oral antihyperglycemic drug	12 436 (18.6)	43 207 (18.2)	0.011	12 217 (18.7)	12 346 (18.9)	−0.005
Diuretics	16 320 (24.4)	60 182 (25.3)	−0.021	16 152 (24.7)	16 374 (25.1)	−0.008
β-Blocker	10 459 (15.6)	51 586 (21.7)	−0.156	10 381 (15.9)	10 495 (16.1)	−0.005
Calcium channel blocker	19 069 (28.5)	76 346 (32.1)	−0.079	18 779 (28.8)	18 942 (29.0)	−0.006
ACEI or ARB	13 732 (20.5)	65 347 (27.5)	−0.163	13 642 (20.9)	13 599 (20.8)	0.002
Statin	3782 (5.6)	24 756 (10.4)	−0.176	3764 (5.8)	3814 (5.8)	−0.003
Steroid	8348 (12.5)	26 230 (11.0)	0.045	8141 (12.5)	8361 (12.8)	−0.010
Cardiovascular risk factors and history						
Diabetes mellitus	45 474 (67.9)	133 556 (56.1)	0.245	43 895 (67.3)	43 922 (67.3)	−0.001
Hypertension	61 290 (91.5)	205 561 (86.4)	0.165	59 617 (91.3)	59 633 (91.4)	−0.001
End-stage renal disease	22 609 (33.8)	47 009 (19.8)	0.320	20 994 (32.2)	20 994 (32.2)	0.000
History						
Cerebrovascular disease	38 512 (57.5)	98 239 (41.3)	0.329	36 969 (56.6)	36 858 (56.5)	0.003
Myocardial infarction	8676 (13.0)	23 722 (10.0)	0.094	8285 (12.7)	8332 (12.8)	−0.002
Coronary artery disease	43 423 (64.8)	139 148 (58.5)	0.131	42 122 (64.5)	42 188 (64.6)	−0.002
Heart failure	32 169 (48.0)	82 600 (34.7)	0.273	30 864 (47.3)	30 964 (47.4)	−0.003
Dyslipidemia	36 074 (53.9)	131 934 (55.4)	−0.032	35 135 (53.8)	35 092 (53.8)	0.001
Valvular heart disease	14 063 (21.0)	44 869 (18.9)	0.054	13 671 (20.9)	13 668 (20.9)	0.000
Cancer	18 216 (27.2)	58 813 (24.7)	0.057	17 761 (27.2)	18 108 (27.7)	−0.012
Drug abuse	1529 (2.3)	6295 (2.6)	−0.023	1512 (2.3)	1563 (2.4)	−0.005

ACEI indicates angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; IQR, interquartile range; NT$, new Taiwan dollars.

We used matched Cox regression models with a conditional approach and stratification, with results reported as hazard ratios (HRs) and 95% CIs for outcomes of the interest by dialysis status. Interaction test between dialysis and outcomes of the interest was also performed. In addition, we conducted subgroup analyses to examine differences in the presence or absence of covariates between sepsis survivors and matched controls. We used the SQL Server 2012 (Microsoft Corporation, Redmond, WA) for data linkage, processing, and sampling, and SAS version 9.3 (SAS Institute, Cary, NC) for propensity score calculation. All other statistical analyses were performed with STATA statistical software (version 12.0; StataCorp, College Station, TX). Statistical significance was defined as 2-sided $P<0.05$.

Results

Characteristics of the Study Population

A total of 554 863 patients with CKD between January 2000 and December 2011 were identified. Among those patients, we identified 123 796 episodes of hospitalization for sepsis. During hospitalization for sepsis, 62 776 (50.7%) patients required ICU admission, 48 365 (39.1%) received mechanical ventilation, and 57 569 (46.5%) received vasoactive agents.

A total of 66 961 patients with CKD, including 44 352 with nondialysis CKD and 22 609 with dialysis, survived through discharge from hospitalization for sepsis and were included in the sepsis cohort. Sepsis survivors with nondialysis CKD were older (mean age 73.6 years) than those with dialysis (mean age 66.3 years). Baseline clinical characteristics and comorbidities between sepsis survivors with nondialysis CKD and dialysis are shown in Table S2. Overall, the mean age of the sepsis cohort was 71.0±13.2 years, and 52.6% of these patients were men. The median Charlson Comorbidity Index score was 8 (interquartile range, 6–10). The prevalence of comorbid conditions was as follows: diabetes mellitus, 67.9%; hypertension, 91.5%; end-stage renal disease, 33.8%; cerebrovascular disease, 57.5%; coronary artery disease, 64.8%; heart failure, 48.0%; dyslipidemia, 53.9%; and cancer, 27.2%. A total of 65 265 patients with CKD and sepsis were matched according to propensity scores with 65 265 nonsepsis hospitalized control patients with similar baseline clinical characteristics (Table 1).

Long-Term Risks of All-Cause Mortality and MACEs

During the mean 2.5-year follow-up period, the incidence rates of all-cause mortality and MACEs in the sepsis cohort were higher than in the control cohort (288.51 versus 177.71 and 47.05 versus 32.1 per 1000 person-years, respectively). The Cox regression model showed that the sepsis cohort had significantly higher risks of subsequent MACEs (HR, 1.42; 95% CI, 1.37–1.47), myocardial infarction (HR, 1.39; 95% CI, 1.32–1.47), ischemic stroke (HR, 1.46; 95% CI, 1.40–1.52), heart failure (HR, 1.55; 95% CI, 1.51–1.59), and all-cause mortality (HR, 1.56; 95% CI, 1.54–1.58), compared with the matched control cohort. When death was considered as a competing risk, the risks of MACEs, ischemic stroke, myocardial infarction, and heart failure remained significantly increased, but were attenuated, in the sepsis cohort. In analyses stratified according to dialysis status, the results remained unchanged in dialysis and nondialysis patients with CKD (Table 2).

Subgroup Analyses of the Risks of Mortality and MACEs

In subgroup analyses (Figure Panel A and Panel B; Tables S3 and S4), the increased risks of all-cause mortality and MACEs remained consistent in the sepsis groups. Compared with matched controls, the effect of sepsis on the risk of all-cause mortality was significantly greater in younger patients, those with lower Charlson Comorbidity Index scores, those without relevant comorbidities (eg, hypertension, diabetes mellitus, dialysis, or heart failure), those with greater numbers of organ failures, those admitted to the ICU, those with shock status, and those who received mechanical ventilator support during hospitalization. However, the effect of sepsis on the higher risk of major CVEs was not noted in some subgroups of patients, such as those with higher numbers of organ failures or shock status.

Discussion

In this large national CKD cohort with long-term and complete follow-up, sepsis survivors had a 1.4-fold higher rate of MACEs and a 1.6-fold higher rate of all-cause mortality than did matched nonsepsis hospitalized controls. The associations were also consistent across dialysis and nondialysis CKD subpopulations. The associations remained significant, but less marked, in analyses that accounted for the competing risk of death. In addition, similar associations were observed in several subgroup analyses, including those conducted according to age, sex, baseline comorbidities, and sepsis severity.

The reported risks of hospitalization for septicemia in US Medicare patients with CKD who were and were not receiving dialysis were 8-fold and 3- to 4-fold greater, respectively, than in patients without CKD,[1] and short-term outcomes after sepsis were substantially worse in nondialysis and dialysis patients with CKD than in the general population.[25,26] However, little is known about the long-term risk of CVD

Table 2. Risks of MACEs and All-cause Mortality Among Sepsis Survivors and the Nonsepsis Control Cohort

	Sepsis Cohort			Control Cohort			Propensity Score–Matched			
							Crude		Competing Risk	
	No. of Events	Person-Years	Incidence Rate*	No. of Events	Person-Years	Incidence Rate*	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
All CKD patients										
MACEs[†‡]	7072	150 296	47.05	6006	187 123	32.10	1.42 (1.37–1.47)	<0.001	1.16 (1.13–1.21)	<0.001
Ischemic stroke[§]	4583	153 420	29.87	3769	189 532	19.89	1.46 (1.40–1.52)	<0.001	1.20 (1.15–1.25)	<0.001
Myocardial infarction[‖]	2927	158 563	18.46	2518	193 504	13.01	1.39 (1.32–1.47)	<0.001	1.13 (1.08–1.20)	<0.001
Heart failure[¶]	11 796	140 892	83.72	9169	181 060	50.64	1.55 (1.51–1.59)	<0.001	1.32 (1.28–1.35)	<0.001
All-cause mortality[#]	46 781	162 144	288.51	34 860	196 164	177.71	1.56 (1.54–1.58)	<0.001	…	
Nondialysis CKD patients										
MACEs[†]	4568	100 171	45.60	3901	125 422	31.10	1.42 (1.36–1.48)	<0.001	1.16 (1.11–1.21)	<0.001
Ischemic stroke	3101	102 001	30.40	2587	126 904	20.39	1.44 (1.37–1.52)	<0.001	1.18 (1.12–1.24)	<0.001
Myocardial infarction	1743	106 051	16.44	1481	130 203	11.37	1.41 (1.32–1.51)	<0.001	1.15 (1.07–1.23)	<0.001
Heart failure	8405	93 099	90.28	6560	121 052	54.19	1.55 (1.50–1.60)	<0.001	1.31 (1.27–1.35)	<0.001
All-cause mortality	31 529	108 183	291.44	23 127	131 845	175.41	1.59 (1.57–1.62)	<0.001	…	
Dialysis patients										
MACEs[†]	2504	50 124	49.96	2105	61 701	34.12	1.43 (1.35–1.52)	<0.001	1.18 (1.11–1.25)	<0.001
Ischemic stroke	1482	51 419	28.82	1182	62 629	18.87	1.49 (1.38–1.61)	<0.001	1.24 (1.15–1.34)	<0.001
Myocardial infarction	1184	52 512	22.55	1037	63 301	16.38	1.36 (1.25–1.48)	<0.001	1.12 (1.03–1.21)	<0.001
Heart failure	3391	47 793	70.95	2609	60 007	43.48	1.56 (1.48–1.64)	<0.001	1.33 (1.26–1.40)	<0.001
All-cause mortality	15 252	53 961	282.65	11 733	64 318	182.42	1.50 (1.47–1.54)	<0.001	…	

CKD indicates chronic kidney disease; MACEs, major adverse cardiovascular events.
*Per 10^3 person-years.
[†]MACEs were defined as a composite of myocardial infarction and ischemic stroke.
[‡]Interaction *P* value for dialysis and MACEs was 0.881.
[§]Interaction *P* value for dialysis and ischemic stroke was 0.497.
[‖]Interaction *P* value for dialysis and myocardial infarction was 0.427.
[¶]Interaction *P* value for dialysis and heart failure was 0.906.
[#]Interaction *P* value for dialysis and all-cause mortality was <0.001.

after discharge from hospitalization for sepsis in the CKD population. Secondary analysis of data from a prospective study[12] that enrolled 2358 dialysis patients in the United States in 1996 and 1997 showed that sepsis or bacteremia, as a time-dependent covariate, was associated with increased future CVEs (including myocardial infarction, congestive heart failure, stroke, and peripheral vascular disease) during a median follow-up period of 3.2 years, but this analysis was limited by the inclusion of a selected population and insufficient power and size. Another study of a US cohort of older patients (aged 65–100 years) on dialysis in 2001 and 2002, which used a self-controlled case series method, showed a significant increase in cardiovascular risk (myocardial infarction and stroke) by 25% in the first 30 days and 18% in the first 90 days after infection-related hospitalization.[11] However, that study did not examine long-term clinical outcomes or include nondialysis patients with CKD or those younger than 65 years. Thus, the results of our study, which included a broad range of patients with CKD, not only provide strong support for existing evidence from patients on dialysis and/or older patients, but also further extend findings to nondialysis patients with CKD and the young and middle-aged population, which has received less attention.

Results of our subgroup analyses suggest that the greater risks of all-cause death and CVEs after sepsis are due to the greater severity of acute sepsis, reflected by factors such as ICU admission, greater number of organ failures, shock status, and receipt of medical ventilation. Yende et al[5] also found that ICU survivors of sepsis from a US Medicare cohort had significantly increased risks of death and CVEs in comparison with hospitalized control patients with infection who were not admitted to the ICU; organ dysfunction and shock status during severe sepsis appeared to slightly, but not significantly, increase cardiovascular risk in that study. The impact of sepsis per se on subsequent cardiovascular risk in the CKD population may be explained in several ways. First,

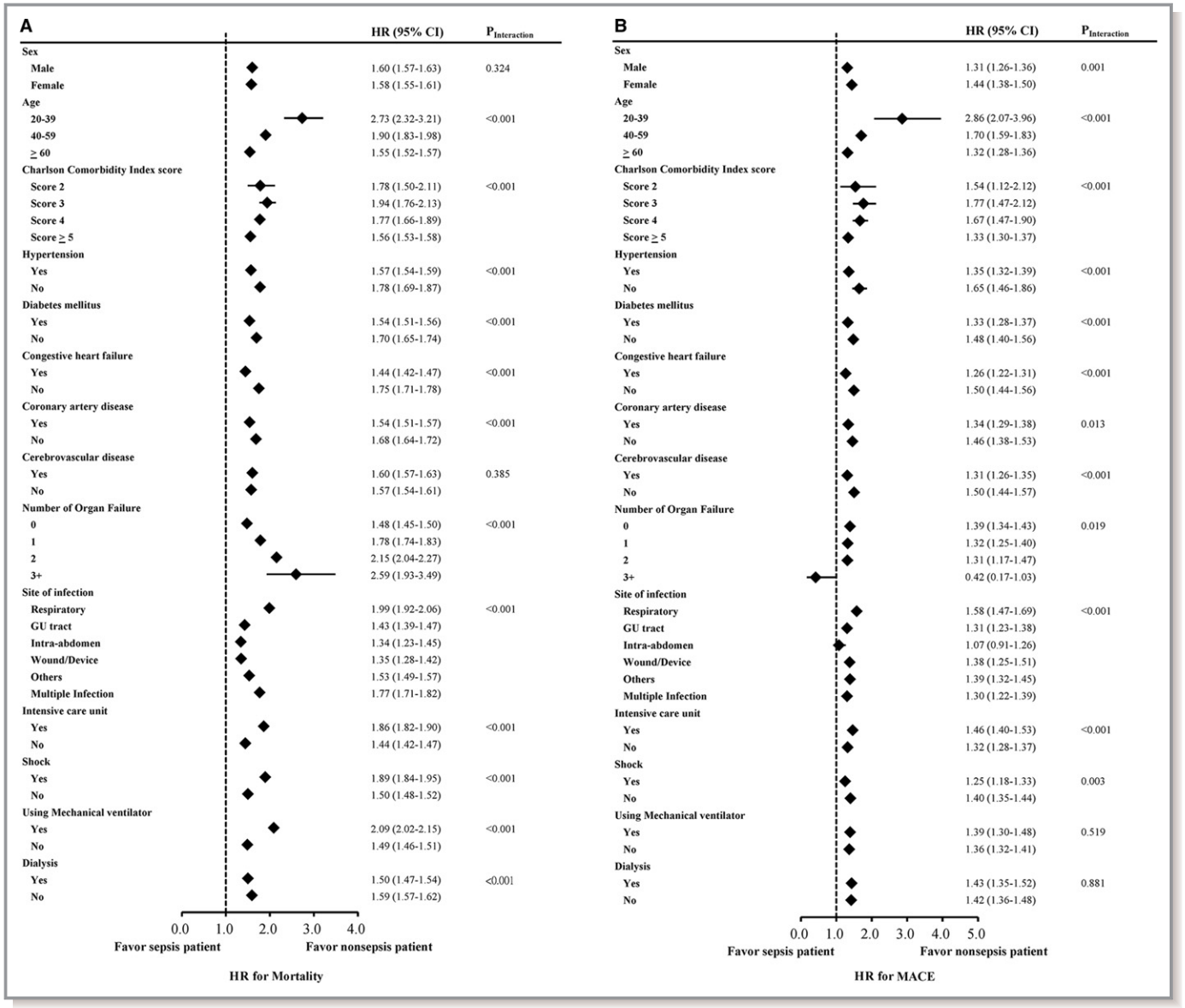

Figure. Subgroup analysis of hazard ratios (HRs) for (A) all-cause mortality and (B) major cardiovascular events (MACEs) among patients with sepsis compared with the matched nonsepsis control cohort.

sepsis may provoke acute kidney injury (AKI), especially in patients with impaired renal function. Despite recovery from acute kidney injury, long-term coronary or stroke risk has been found to persist following acute kidney injury episodes.[27,28] Second, chronic inflammation has been shown to contribute to the link between CKD and CVD.[29] Discharge from hospitalization for sepsis does not necessarily represent complete clinical remission of sepsis; ongoing subclinical inflammation[30] may aggravate the progress of atherosclerosis or increase vulnerability to atherosclerotic plaques, especially in at-risk populations with CKD.[31,32] These adverse influences of sepsis-related inflammation may provide important molecular clues (including data on cytokines, radicals, or adhesion molecules) regarding the pathogenesis of CVEs.[33]

Study Limitations

Our study has several limitations. First, definition of the primary exposure and outcomes was based on ICD-9-CM codes, rather than clinical diagnostic criteria, although the accuracy of these codes has been validated. Thus, potential misclassification or the presence of subclinical disease is of concern; however, we believed that any misclassification is nondifferential for the sepsis and control cohorts, and that the undetected presence of subclinical disease would more likely lead to underestimation of the associations examined. Second, the retrospective observational study design prevented examination of the underlying causality of associations between sepsis and CVD. Third, detailed information on

in-hospital parameters, such as APACHE II scores, biochemical data, and inflammatory markers, was not available in our health insurance claims database. We performed subgroup analyses based on the number of organ failures, site of infection, ICU admission, shock status, and receipt of ventilation as proxies for estimated sepsis severity. Finally, data on sepsis survivors' functional or cognitive status at hospital discharge were not included in our dataset. Nonetheless, we collected comprehensive registry data on demographic characteristics, comorbidities, and concomitant medication use after discharge from hospitalization for sepsis to serve as an overview of individual complexity.

Conclusions

Our findings underline the significant long-term cardiovascular consequences in patients with CKD who have survived sepsis. We urge physicians to increase vigilance related to modifiable cardiovascular risk factors in these patients, which may help to improve overall post-sepsis clinical outcomes. Further research is required to elucidate the nature of the interaction between sepsis and subsequent CVEs and to facilitate the identification of novel targets for intervention that can mitigate these adverse consequences in patients with CKD.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Propensity Score Model Results of Probability of Diagnosis of Sepsis.

			95% CI		
Parameter	**Estimate**	**Odds Ratios**	**Lower**	**Upper**	**P value**
Age, per year	-0.0648	0.937	0.936	0.939	<.0001
Year of Index Date					
2000		1			
2001	-0.1364	0.873	0.759	1.003	0.0543
2002	-0.4162	0.66	0.576	0.756	<.0001
2003	-0.4079	0.665	0.581	0.761	<.0001
2004	-0.5318	0.588	0.516	0.669	<.0001
2005	-0.5806	0.56	0.493	0.635	<.0001
2006	-0.5446	0.58	0.511	0.658	<.0001
2007	-0.5296	0.589	0.52	0.667	<.0001
2008	-0.5282	0.59	0.521	0.668	<.0001
2009	-0.5003	0.606	0.536	0.686	<.0001
2010	-0.515	0.598	0.529	0.675	<.0001
2011	-0.5152	0.597	0.529	0.674	<.0001
Month of Index Date					
January		1			
February	0.0372	1.038	0.936	1.15	0.4783
March	0.071	1.074	0.97	1.188	0.1701
April	0.097	1.102	0.997	1.218	0.0572
May	0.0987	1.104	1	1.219	0.051
June	0.0696	1.072	0.971	1.184	0.1686
July	0.0593	1.061	0.963	1.17	0.233
August	0.0456	1.047	0.95	1.153	0.3581
September	0.0576	1.059	0.961	1.168	0.2469
October	-0.00072	0.999	0.906	1.102	0.9886
November	-0.0242	0.976	0.884	1.077	0.6306
December	-0.0225	0.978	0.887	1.078	0.653
Male	-0.4172	0.659	0.633	0.686	<.0001
Monthly income, NT$					
Dependent		1			
<19,100	-0.2497	0.779	0.74	0.82	<.0001
19,100–42,000	-0.0171	0.983	0.94	1.028	0.4575
> 42,000	0.3669	1.443	1.22	1.707	<.0001
Urbanization level*					
1		1			

2	-0.1588	0.853	0.817	0.891	<.0001
3	-0.1758	0.839	0.764	0.921	0.0002
4 (rural)	-0.1379	0.871	0.72	1.054	0.1552
Charlson comorbidity index score†	-0.0326	0.968	0.958	0.978	<.0001
Duration of chronic kidney disease, month	-0.00075	0.999	0.999	1	0.0053
Concomitant medications					
Antiplatelet	0.12	1.128	1.073	1.185	<.0001
Insulin	0.5098	1.665	1.564	1.772	<.0001
Oral anti-hyperglycemic drug	-0.5067	0.602	0.57	0.637	<.0001
Diuretics	-1.6454	0.193	0.182	0.205	<.0001
Beta-blocker	0.2404	1.272	1.199	1.349	<.0001
Calcium channel blocker	0.0445	1.046	0.997	1.096	0.0647
ACEI/ARB	-0.3339	0.716	0.678	0.756	<.0001
Statin	0.0814	1.085	0.99	1.188	0.0797
Steroid	-0.4215	0.656	0.617	0.698	<.0001
Coexisting conditions					
Cerebrovascular disease	-0.2367	0.789	0.754	0.826	<.0001
Hypertension	1.3331	3.793	3.486	4.127	<.0001
Myocardial infarction	0.0495	1.051	0.99	1.115	0.1043
Coronary artery disease	0.1851	1.203	1.149	1.26	<.0001
Heart failure	0.7355	2.087	1.996	2.181	<.0001
Peripheral vascular disease	0.3968	1.487	1.411	1.567	<.0001
Chronic liver disease	-0.1933	0.824	0.79	0.86	<.0001
Dyslipidemia	-0.0892	0.915	0.876	0.954	<.0001
Valvular heart disease	0.0767	1.08	1.029	1.133	0.0019
Diabetes mellitus	0.2909	1.338	1.271	1.408	<.0001
Cancer	0.069	1.071	1.015	1.131	0.0131
Drug abuse	-1.027	0.358	0.31	0.413	<.0001

*Urbanization levels in Taiwan are divided into four strata according to the Taiwan National Health Research Institute publications. Level 1 designates the most urbanized areas, and level 4 designates the least urbanized areas.

†Charlson Comorbidity Index (CCI) score is used to determine overall systemic health. With each increased level of CCI score, there are stepwise increases in the cumulative mortality.

Abbreviations: NT$, new Taiwan dollars.

Table S2. Demographic and Clinical Characteristics of the CKD Patients with and without dialysis Who were Hospitalized with a Diagnosis of Sepsis

	CKD patients		
Characteristic	**With dialysis**	**Without dialysis**	**P value**
Number of patients	22,609	44,352	
Mean age (SD), years	66.3 (13.1)	73.6 (12.5)	<0.001
Males	10,492 (46.4)	24,357 (54.9)	<0.001
Monthly income, NT$			
Dependent	9,031 (39.9)	17,274 (38.9)	<0.001
<19,100	4,724 (20.9)	11,348 (25.6)	
19,100–42,000	8,357 (37.0)	15,273 (34.4)	
> 42,000	497 (2.2)	457 (1.0)	
Urbanization level			
1	7,173 (31.7)	12,308 (27.8)	<0.001
2	14,125 (62.5)	29,296 (66.1)	
3	1,079 (4.8)	2,297 (5.2)	
4 (rural)	232 (1.0)	451 (1.0)	
Charlson Comorbidity Index score, median (IQR)	8 (6-10)	8 (6-10)	<0.001
Concomitant medications			
Antiplatelet agent	5,093 (22.5)	11,018 (24.8)	<0.001
Insulin	3,322 (14.7)	4,824 (10.9)	<0.001
Oral anti-hyperglycemic drug	3,291 (14.6)	9,145 (20.6)	<0.001
Diuretics	2,299 (10.2)	14,021 (31.6)	<0.001
Beta-blocker	3,771 (16.7)	6,688 (15.1)	<0.001
Calcium channel blocker	6,053 (26.8)	13,016 (29.3)	<0.001
ACEI or ARB	3,984 (17.6)	9,748 (22.0)	<0.001
Statin	1,294 (5.7)	2,488 (5.6)	<0.001
Steroid	2,189 (9.7)	6,159 (13.9)	<0.001
CV risk factors and history			
Diabetes mellitus	15,802 (69.9)	29,672 (66.9)	<0.001
Hypertension	21,362 (94.5)	39,928 (90.0)	<0.001
History of			
Cerebrovascular disease	11,528 (51.0)	26,984 (60.8)	<0.001
Myocardial infarction	3,002 (13.3)	5,674 (12.8)	<0.001
Coronary artery disease	14,694 (65.0)	28,729 (64.8)	<0.001
Heart failure	12,100 (53.5)	20,069 (45.2)	<0.001
Dyslipidemia	12,247 (54.2)	23,827 (53.7)	<0.001

Valvular heart disease	4,795 (21.2)	9,268 (20.9)	<0.001
Cancer	5,581 (24.7)	12,635 (28.5)	<0.001
Drug abuse	313 (1.4)	1,216 (2.7)	<0.001

Abbreviations: SD, standard deviation; NT$, new Taiwan dollars; IQR, interquartile range; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker ;CV, cardiovascular; CKD, chronic kidney disease

Table S3. Subgroup analysis of Risk of All-cause Mortality among Subjects with Sepsis and Matched Hospitalized Control Cohort

Characteristic	Adjusted*		
	Hazard Ratio (95% CI)	*P* Value	Interaction *P* Value
Sex			
Male	1.597 (1.567-1.628)	<0.001	0.324
Female	1.579 (1.546-1.612)	<0.001	
Age			
20-39	2.732 (2.324-3.211)	<0.001	<0.001
40-59	1.903 (1.827-1.983)	<0.001	
≥ 60	1.545 (1.523-1.569)	<0.001	
Charlson Comorbidity Index score			
Score 2	1.780 (1.498-2.114)	<0.001	<0.001
Score 3	1.938 (1.762-2.132)	<0.001	
Score 4	1.770 (1.656-1.893)	<0.001	
Score ≥ 5	1.556 (1.534-1.579)	<0.001	
Hypertension			
Yes	1.567 (1.544-1.590)	<0.001	<0.001
No	1.776 (1.689-1.867)	<0.001	
Diabetes mellitus			
Yes	1.535 (1.510-1.561)	<0.001	<0.001
No	1.695 (1.653-1.738)	<0.001	
Congestive heart failure			
Yes	1.444 (1.417-1.472)	<0.001	<0.001
No	1.748 (1.713-1.783)	<0.001	
Coronary artery disease			
Yes	1.539 (1.513-1.565)	<0.001	<0.001
No	1.683 (1.642-1.724)	<0.001	
Cerebrovascular disease			
Yes	1.601 (1.572-1.629)	<0.001	0.385
No	1.574 (1.539-1.609)	<0.001	
Number of Organ Failure			
0	1.478 (1.454-1.504)	<0.001	<0.001
1	1.784 (1.735-1.834)	<0.001	
2	2.149 (2.036-2.269)	<0.001	
3+	2.594 (1.928-3.488)	<0.001	
Site of infection			

Respiratory	1.986 (1.918-2.057)	<0.001	<0.001
GU tract	1.426 (1.385-1.469)	<0.001	
Intra-abdomen	1.338 (1.233-1.453)	<0.001	
Wound/Device	1.346 (1.278-1.418)	<0.001	
Others	1.530 (1.493-1.568)	<0.001	
Multiple Infection	1.766 (1.711-1.823)	<0.001	
Intensive care unit			
Yes	1.858 (1.817-1.900)	<0.001	<0.001
No	1.442 (1.416-1.468)	<0.001	
Shock			
Yes	1.894 (1.841-1.948)	<0.001	<0.001
No	1.500 (1.476-1.524)	<0.001	
Using Mechanical ventilator			
Yes	2.086 (2.023-2.151)	<0.001	<0.001
No	1.487 (1.464-1.510)	<0.001	

* Adjusted for propensity score.

Abbreviations: CI, confidence interval; GU, genitourinary.

Table S4. Subgroup analysis of Risk of Major Cardiovascular Events among Subjects with Sepsis and Matched Hospitalized Control Cohort

Characteristic	Adjusted*		
	Hazard Ratio (95% CI)	*P* Value	Interaction *P* Value
Sex			
Male	1.311 (1.263-1.361)	<0.001	0.001
Female	1.438 (1.382-1.496)	<0.001	
Age			
20-39	2.860 (2.068-3.956)	<0.001	<0.001
40-59	1.703 (1.587-1.828)	<0.001	
≥ 60	1.317 (1.278-1.356)	<0.001	
Charlson Comorbidity Index score			
Score 2	1.539 (1.119-2.117)	0.008	<0.001
Score 3	1.765 (1.472-2.117)	<0.001	
Score 4	1.667 (1.465-1.896)	<0.001	
Score ≥ 5	1.333 (1.296-1.372)	<0.001	
Hypertension			
Yes	1.352 (1.315-1.390)	<0.001	<0.001
No	1.647 (1.456-1.863)	<0.001	
Diabetes mellitus			
Yes	1.325 (1.284-1.367)	<0.001	<0.001
No	1.481 (1.404-1.563)	<0.001	
Congestive heart failure			
Yes	1.263 (1.218-1.310)	<0.001	<0.001
No	1.496 (1.437-1.558)	<0.001	
Coronary artery disease			
Yes	1.336 (1.294-1.380)	<0.001	0.013
No	1.456 (1.384-1.532)	<0.001	
Cerebrovascular disease			
Yes	1.308 (1.264-1.353)	<0.001	<0.001
No	1.504 (1.438-1.574)	<0.001	
Number of Organ Failure			
0	1.387 (1.344-1.433)	<0.001	0.019
1	1.321 (1.249-1.398)	<0.001	
2	1.311 (1.166-1.474)	<0.001	
3+	0.416 (0.168-1.027)	0.057	
Site of infection			

Respiratory	1.576 (1.470-1.690)	<0.001	<0.001
GU tract	1.305 (1.232-1.382)	<0.001	
Intra-abdomen	1.073 (0.912-1.262)	0.396	
Wound/Device	1.377 (1.253-1.513)	<0.001	
Others	1.386 (1.324-1.452)	<0.001	
Multiple Infection	1.303 (1.220-1.391)	<0.001	
Intensive care unit			
Yes	1.461 (1.397-1.529)	<0.001	<0.001
No	1.319 (1.275-1.365)	<0.001	
Shock			
Yes	1.249 (1.177-1.325)	<0.001	0.003
No	1.396 (1.354-1.439)	<0.001	
Using Mechanical ventilator			
Yes	1.388 (1.300-1.482)	<0.001	0.519
No	1.364 (1.323-1.405)	<0.001	

* Adjusted for propensity score.

Abbreviations: CI, confidence interval; GU, genitourinary.