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Letter to the Editor

LETTER TO THE EDITOR

Statin use and survival among ESKD patients hospitalized with sepsis

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Sepsis is a common cause of mortality in hospitalized patients in the USA and worldwide [1]. Among patients with end-stage kidney disease (ESKD), sepsis is the second most common known cause of mortality, trailing only mortality from cardiac causes [2]. Sepsis is presumed to arise from the dysregulation of the immune response to infection [3]. Although standard treatment relies on maintaining tissue perfusion and initiation of empiric antibiotics, statins have been implicated as having a potential mortality benefit in sepsis [4].

Widely known for their lipid-lowering properties, statins are also thought to have inherent anti-inflammatory properties [5]. Although chronic kidney disease is a risk-enhancing factor for atherosclerotic cardiovascular disease, the most recent guidelines provided by the American Heart Association do not recommend the initiation of statins for adults requiring dialysis treatment based on lack of cardiovascular benefit [6]. Supporting this guideline, rosuvastatin was shown not to have a significant benefit in composite cardiovascular death, nonfatal myocardial infarction and stroke in patients receiving hemodialysis [7]. However, to date, studies have not investigated whether statins affect sepsis mortality in the ESKD population. Thus, we sought to determine whether chronic statin use was associated with mortality benefits among ESKD patients hospitalized for sepsis within the Kaiser Permanente Southern California (KPSC) healthcare system.

A retrospective cohort study was performed among patients admitted to the hospital with a diagnosis of both sepsis and ESKD [obtained through the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) and ICD-10-CM] between 1 January 2008 and 30 September 2018. The KPSC ESKD population is racially/ethnically diverse and generally reflective of the KPSC membership population [8, 9]. Statin users were defined as those having filled two prescriptions for a statin within 6 months prior to admission, with the second prescription filled within 30 days prior to admission based on the KPSC pharmacy and analytic database. The primary outcome of 30-day all-cause mortality was analyzed unweighted and weighted using the Inverse Probability Treatment Weighting (IPTW) method.

A total of 8858 patients were included in our study, with 2820 on statins and 6038 not on statins at the time of admission for sepsis. At baseline, there were differences between statin users and non-users in age, sex, race and comorbidities such as heart disease, hypertension, cerebrovascular disease and diabetes (Table 1). Thus, we used the IPTW method to create synthetic groups to more adequately compare the effect of statin exposure. After IPTW, statin users and non-users were similar across many of the covariates analyzed such as sex, race, heart failure, ischemic heart disease, cerebrovascular disease and renin angiotensin system blocker use. However, significant differences between statin users and non-users remained for

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Table 1. Patient characteristics before and after IPTW

	Unweighted				Weighted			
		Statin user				Statin user		
	Total	Yes	No	P-value	Total	Yes	No	P-value
N	8858	2820	6038		8858	2820	6038	
Age, years								
<45	703 (7.9)	101 (3.6)	602 (10.0)	<0.0001	671 (7.6)	193 (6.8)	478 (7.9)	0.0543
45–64	2999 (33.9)	774 (27.4)	2225 (36.8)		2951 (33.3)	914 (32.4)	2038 (33.7)	
≥65	5156 (58.2)	1945 (69.0)	3211 (53.2)		5236 (59.1)	1713 (60.8)	3523 (58.3)	
Sex				0.0249				0.4299
Female	3765 (42.5)	1150 (40.8)	2615 (43.3)		3799 (42.9)	1227 (43.5)	2572 (42.6)	
Male	5093 (57.5)	1670 (59.2)	3423 (56.7)		5059 (57.1)	1593 (56.5)	3466 (57.4)	
Race				<0.0001				0.9226
White	2762 (31.2)	1011 (35.9)	1751 (29.0)		2759 (31.2)	874 (31.0)	1885 (31.2)	
Black	1885 (21.3)	520 (18.4)	1365 (22.6)		1883 (21.3)	600 (21.3)	1283 (21.2)	
Hispanic	3070 (34.7)	858 (30.4)	2212 (36.6)		3054 (34.5)	963 (34.2)	2091 (34.6)	
Asian	1048 (11.8)	408 (14.5)	640 (10.6)		1070 (12.1)	354 (12.5)	716 (11.9)	
Other[a]	93 (1.1)	23 (0.8)	70 (1.2)		92 (1.0)	29 (1.0)	63 (1.1)	
Comorbidity								
Liver disease	1406 (15.9)	321 (11.4)	1085 (18.0)	<0.0001	1353 (15.3)	399 (14.2)	954 (15.8)	**0.0439**
Heart failure	4771 (53.9)	1649 (58.5)	3121 (51.7)	<0.0001	4837 (54.6)	1580 (56)	3256 (53.9)	0.0636
Chronic pulmonary disease	2051 (23.2)	678 (24.0)	1373 (22.7)	0.1756	2068 (23.3)	666 (23.6)	1403 (23.2)	0.7016
Ischemic heart disease	4709 (53.2)	1731 (61.4)	2978 (49.3)	<0.0001	4781 (54)	1562 (55.4)	3218 (53.3)	0.0638
Rheumatological disease	148 (1.7)	47 (1.7)	101 (1.7)	0.9834	147 (1.7)	45 (1.6)	102 (1.7)	0.8007
Hypertension	8460 (95.5)	2788 (98.9)	5672 (93.9)	<0.0001	8510 (96.1)	2742 (97.2)	5768 (95.5)	**0.0001**
Cerebrovascular disease	1169 (13.2)	404 (14.3)	765 (12.7)	0.0319	1190 (13.4)	395 (14)	795 (13.2)	0.2798
Diabetes mellitus	6745 (76.2)	2328 (82.6)	4417 (73.2)	<0.0001	6868 (77.5)	2259 (80.1)	4609 (76.3)	**0.0001**
Dementia	833 (9.4)	268 (9.5)	565 (9.4)	0.8262	847 (9.6)	278 (9.9)	569 (9.4)	0.5062
Malnutrition	4458 (50.3)	1382 (49.0)	3076 (50.9)	0.0894	4475 (50.5)	1438 (51)	3037 (50.3)	0.5458
Peptic ulcer disease	529 (6.0)	173 (6.1)	356 (5.9)	0.6587	522 (5.9)	164 (5.8)	358 (5.9)	0.8545
Any malignancy	4585 (51.8)	1616 (57.3)	2969 (49.2)	<0.0001	4569 (51.6)	1447 (51.3)	3121 (51.7)	0.740
Prior transplantation	1508 (17.0)	522 (18.5)	986 (16.3)	0.011	1490 (16.8)	470 (16.7)	1020 (16.9)	0.795
History of GI hemorrhage	2224 (25.1)	685 (24.3)	1539 (25.5)	0.2259	2214 (25)	697 (24.7)	1517 (25.1)	0.688
Alcohol/drug use	987 (11.1)	221 (7.8)	766 (12.7)	<0.0001	944 (10.7)	276 (9.8)	668 (11.1)	0.0647
AIDS/HIV	54 (0.6)	16 (0.6)	38 (0.6)	0.727	52 (0.6)	16 (0.6)	36 (0.6)	0.7771
Hyperlipidemia	7602 (85.8)	2734 (97.0)	4868 (80.6)	<0.0001	7688 (86.8)	2503 (88.8)	5184 (85.9)	**0.0002**
Cardiovascular medications								
Digoxin	392 (4.4)	147 (5.2)	245 (4.1)	0.0138	398 (4.5)	127 (4.5)	271 (4.5)	0.9815
Beta-blockers	6032 (68.1)	2176 (77.2)	3856 (63.9)	<0.0001	6121 (69.1)	2000 (70.9)	4121 (68.2)	**0.0107**
ACE inhibitors	3090 (34.9)	1110 (39.4)	1980 (32.8)	<0.0001	3122 (35.3)	1009 (35.8)	2114 (35)	0.477
Angiotensin receptor blockers	1937 (21.9)	716 (25.4)	1221 (20.2)	<0.0001	1979 (22.3)	653 (23.1)	1326 (22)	0.2123
Immunosuppressants								
Biologics	1106 (12.5)	417 (14.8)	689 (11.4)	<0.0001	1105 (12.5)	353 (12.5)	753 (12.5)	0.9664
Oral corticosteroids	2499 (28.2)	894 (31.7)	1605 (26.6)	<0.0001	2521 (28.5)	811 (28.8)	1710 (28.3)	0.6779
DMARDs	251 (2.8)	83 (2.9)	168 (2.8)	0.6708	253 (2.9)	79 (2.8)	173 (2.9)	0.8696

[a]Including multiple, Native American, Alaskan, other or unknown race. P-value was generated by Chi-square test for categorical variables and Kruskal–Wallis test. Data are presented as *n* (%). GI, gastrointestinal; ACE, angiotensin-converting enzyme; DMARDs, disease-modifying anti-rheumatic drugs. Bolded values were considered significant as P-value <0.05.

hypertension, diabetes, hyperlipidemia and use of beta-blockers (Table 1).

Analysis of the IPTW 30-day mortality hazard ratio for ESKD patients hospitalized for sepsis demonstrated a mortality hazard ratio (HR) of 0.82 [95% confidence interval (CI) 0.74–0.91] for statin users compared with non-users. A similar effect was observed using an unweighted comparison, with a HR of 0.85 (95% CI 0.77–0.91). Furthermore, the effect persisted when comparing mortality between statin users and non-users at 90 days with a HR of 0.82 (95% CI 0.76–0.90) and 0.86 (95% CI 0.76–0.90) for weighted and unweighted comparisons, respectively.

Our findings from a real-world population suggest that statin use is associated with lower mortality among ESKD patients hospitalized for sepsis. A strength of our study includes the large, diverse patient population obtained through the comprehensive electronic health records. Potential limitations of our study include the fact that we were not able to fully propensity match certain covariates such as hypertension, diabetes and hyperlipidemia between statin users and non-users, which may confound the interpretation of our findings. In addition, we did not have information on type of dialysis access (fistulas, grafts and catheters)

for the entire study population. Nonetheless, our study sheds light on the potential benefits of statins in the ESKD population, a population that is highly prone to infections and infection-related mortality. Although previous studies have not demonstrated a cardiovascular mortality benefit from statin use in ESKD patients, statins have been shown to provide a mortality benefit in a subset of the ESKD population, such as those with acute myocardial infarction [10]. While additional studies are warranted, our findings suggest a potential benefit of statins for ESKD patients hospitalized for sepsis, a population that is highly susceptible to infections.

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CONFLICT OF INTEREST STATEMENT

None of the authors has any conflicts of interest relevant to this manuscript. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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