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Statins improve the long-term prognosis in patients who have survived sepsis

A nationwide cohort study in Taiwan (STROBE complaint)

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Abstract

Most patients diagnosed with sepsis died during their first episode, with the long-term survival rate upon post-sepsis discharge being low. Major adverse cardiovascular events and recurrent infections were regarded as the major causes of death. No definite medications had proven to be effective in improving the long-term prognosis. We aimed to examine the benefits of statins on the long-term prognosis of patients who had survived sepsis.

Between 1999 and 2013, a total of 220,082 patients who had been hospitalized due to the first episode of sepsis were included, with 134,448 (61.09%) of them surviving to discharge. The surviving patients who were subsequently prescribed statins at a concentration of more than 30 cumulative Defined Daily Doses (cDDDs) during post-sepsis discharge were defined as the users of statin.

After a propensity score matching ratio of 1:5, a total of 7356 and 36,780 surviving patients were retrieved for the study (statin users) and comparison cohort (nonstatin users), respectively. The main outcome was to determine the long-term survival rate during post-sepsis discharge.

HR with 95% CI was calculated using the Cox regression model to evaluate the effectiveness of statins, with further stratification analyses according to cDDDs.

The users of statins had an adjusted HR of 0.29 (95% CI, 0.27–0.31) in their long-term mortality rate when compared with the comparison cohort. For the users of statins with cDDDs of 30–180, 180–365, and >365, the adjusted HRs were 0.32, 0.22, and 0.16, respectively, (95% CI, 0.30–0.34, 0.19–0.26, and 0.12–0.23, respectively), as compared with the nonstatins users (defined as the use of statins <30 cDDDs during post-sepsis discharge), with the *P* for trend <.0001. In the sensitivity analysis, after excluding the surviving patients who had died between 3 and 6 months after post-sepsis discharge, the adjusted HR for the users of statins remained significant (0.35, 95% CI 0.32–0.37 and 0.42, 95% CI 0.39–0.45, respectively).

Statins may have the potential to decrease the long-term mortality of patients who have survived sepsis. However, more evidence, including clinical and laboratory data, is necessary in order to confirm the results of this observational cohort study.

Trial registration: CMUH104-REC2-115.

Abbreviations: ATC = anatomical therapeutic chemical, CCI score = Charlson Comorbidity Index score, cDDDs = cumulative defined daily doses, CHF = congestive heart failure, CI = confidence interval, CKD = chronic kidney disease, CLD = chronic liver disease, Clinical Modification, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, eNOS = endothelial nitric oxide synthase, HR = hazard ratio, HTN = hypertension, ICD-9-CM = International Classification of Diseases, ICU = intensive care

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unit, IHD = ischemic heart disease, IR: incidence rate, MACEs = major cardiovascular events, NHIA = National Health Insurance Administration, NHIRD = National Health Insurance Research Database, Ninth Revision, NSAID = non-steroid anti-inflammatory drug, NT$ = New Taiwan Dollar.

Keywords: 3-hydroxy-3-methylglutaryl-coenzyme-A inhibitors, sepsis

1. Introduction

Sepsis, a complex syndrome caused by infections and possessing an unregulated immune response, is a leading cause of mortality worldwide.[1–3] Despite the advancements in medical care, the mortality rate remains high, ranging from 17% to 26% in varied severity and countries.[2] It has been demonstrated that the patients who have survived sepsis possessed an increased subsequent long-term risk of Major Cardiovascular Events (MACEs), along with an associated lower survival rate when compared with the general population.[4–6] Maintenance of long-term post-sepsis survival and being free from its complications, such as MACEs or recurrent infections, remains a great challenge.[7–9] Currently, few studies propose effective interventions or medications to prevent this compromised course.

Statins (3-hydroxy-3-methylglutaryl-coenzyme-A inhibitors) are widely used in treating hypercholesterolemia, and therefore reduce the risk of cardio- and cerebro-vascular diseases. Statins have also been proven to have antiinflammatory and immunomodulation effects, including the reduction of inflammatory cytokines, chemotaxis, and neutrophil migration.[10,11] Due to of the proposed pleiotropic immunomodulatory effects of statins, a large number of observational studies and randomized control trials were conducted, from the years 2004 to 2013.[12] However, the effects of statins remain a major controversy; most RCTs showed no benefits regarding statins in mortality during sepsis, while observational studies have shown a protective effect. Recently, because of the new publication on bactericidal effects of statins, and a decreased risk of mycobacterium tuberculosis infection, the use of statins in sepsis has raised new attention.[13] Furthermore, it has also been proposed in recent days that different types of statins had exerted varied protective effects for sepsis, thus exploring a new prospective future.[14]

In light of a rise in incidence and a falling fatality rate, improving the long-term outcome amongst sepsis survivors has become increasingly important.[15] In this current study, we hypothesized that statin use may improve long-term outcomes during the first episode for patients who had survived sepsis, via its potential secondary prevention in cardio- and cerebro-vascular diseases and recurrent infections. This nationwide population-based cohort study was conducted by using the National Health Insurance Research Database of Taiwan (NHIRD).

2. Methods

2.1. Ethics approval and consent to participate

This study was conducted by using the NHIRD in Taiwan. The NHIRD contained de-identified secondary data for research. Our study was exempted from the requirement of obtaining informed consent from participants. This study was approved by the Institutional Review Board of China Medical University (CMUH104-REC2-115).

2.2. Patients and public involvement

We conducted this nationwide cohort study using data from the NHIRD. The National Health Insurance program was launched in 1995 in Taiwan by the National Health Insurance Administration (NHIA) and provided coverage for >23.03 million residents (99.2% of the entire population). The NHIA released identification-encrypted claims data to the National Health Research Institute and established the NHIRD. Data confidentiality was strictly maintained in accordance with the regulations of NHIRD.

In the NHIRD, the diagnosis codes of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) were used to identify specific diagnoses. The patients of sepsis were retrieved from the database by using the ICD-9-CM codes 038, 995.91, and A038. The specificity of the diagnosis of sepsis in the NHIRD had been validated in previous studies.[7] The statins of interest in this study were retrieved from the claims data by the codes of C10AA, C10BA, and C10BX through the Anatomical Therapeutic Chemical (ATC) Classification System.

The first episode of sepsis necessitating admission throughout the study, was defined as the index hospitalization. The index date was defined as the post-sepsis discharge date of the index hospitalization due to sepsis. The associated comorbid conditions were also identified by using the ICD-9-CM codes; the diagnoses prior to or in concurrence with the index hospitalization due to sepsis were considered as the underlying comorbidities.

The patients were categorized as taking a certain kind of drug if they took them for more than 1 month within a 3-month period, prior to the index hospitalization. The immunosuppressants, including cyclosporin, everolimus, mycophenolic acid, sirolimus, and tacrolimus, were also taken into consideration in this current study.

We defined the specific managements and procedures during hospitalization by using the patient's claims information for insurance charges, and these included (1) inotropic agent use, (2) Intensive Care Unit (ICU) admission (claims codes: 02011K, 02012A, 02013B, 03010E, 03011F, 03012G, 03047E, 03048F, and 03049G in the NHIRD), and (3) receiving mechanical ventilation (claims code of 57001B).

Initially, we used the NHIRD to retrieve patients who had survived the first episode of sepsis between 1999 and 2012. The claims data from the NHIRD were from the years 1999 to 2013, therefore allowing for all the enrolled patients to be followed up for at least 1 year.

In this current study, we categorized the users of statins into four groups according to their cumulative Defined Daily Doses (cDDDs): <30, 30–180, 180–365, and >365 cDDDs during the follow-up period because the duration of the drug refill card in Taiwan was 3 months. The study cohort was defined as those patients who had the use of statins for >30 cDDDs and had survived discharge after the first episode of sepsis, with the cDDDs calculated from the index date. The comparison cohort

was composed of the nonstatin users or statin users of <30 cDDDs. In this current study, we also defined the use of statins <30 cDDDs as the nonstatin users.

To avoid the bias from selection, we matched patients of this study and those in the comparison cohort through the use of propensity score matching. The propensity scores used in this study were composed of multiple variables of interest, such as age, gender, socioeconomic status, level of urbanization, and baseline comorbidities, which were calculated via logistic regression. Propensity score matching was able to reduce the selection bias because it was capable of bundling many confounding covariates which were presented in an observational study.

Data providing socioeconomic status, level of urbanization, and residential area were obtained directly from the database. We used the paid insurance premiums as a proxy to determine the level of household income and socio-economic backgrounds. We further classified this data into four categories. Those with well-defined monthly salaries were grouped into four categories: (1) less than NT$ (New Taiwan Dollar) 20,000, (2) NT$ 20,000 to NT$ 40,000, (3) NT$ 40,000 to NT$ 60,000, and (4) more than NT$ 60,000.

The patients who had been a final diagnosis of diabetes mellitus were enrolled for the observational cohort study. The selection process of participants from the nationwide database was shown in Supplement Figure 1, http://links.lww.com/MD/C935. Any sepsis patients aged <20 or >100 years, and those infected with human immunodeficiency virus, were excluded from this study. Since the NHIRD contained de-identified secondary data for the purpose of research, our study was exempted from the requirement of obtaining informed consent from participants.

2.3. Main outcomes and measures

The main outcome was to determine the long-term survival rate after index hospitalization between the study group (users of statins >30 cDDDs) and comparison cohorts (nonusers or users of statins <30 cDDDs).

Further comparisons were then conducted to compare the long-term survival rate within the study cohort for those given different cumulative doses (cDDDs of 30–180, 180–365, and >365). Hazard ratios (HRs) with a 95% Confidence Intervals (95% CIs) were calculated using the Cox proportional hazards regression model.

2.4. Sensitivity analysis

Since most patients of sepsis are re-hospitalized after discharge and soon die, and as we mainly focused on the long-term protective effect of statins, we conducted one sensitivity analysis after excluding mortality cases within 3 months of post-sepsis discharge and another sensitivity analysis after excluding mortality cases within 6 months of post-sepsis discharge. We excluded those patients who had survived discharge after their first episode of sepsis, but died between 3 and 6 months after post-sepsis discharge.

2.5. Statistical analysis

Differences in demographic characteristics, comorbidities, medications, and socioeconomic status were examined by using χ^2 tests for noncontinuous variables, along with two-sample Student's *t*-tests for continuous variables. HRs with 95% CIs were calculated for each variable using Cox proportional hazard regression. Adjusted HRs for mortality were obtained after adjustment for possible confounders. Kaplan–Meier analyses with log-rank test were conducted to compare the long-term survival rates between the study and comparison cohorts.

The statistical analyses were performed using SAS 9.4 statistical package (SAS Institute Inc., Cary, NC, USA). A forest plot was created using Microsoft Excel 2010 (Microsoft, Redmond, WA, USA). A *P* value of .05 was considered significant.

3. Results

Taken from the NHIRD between 1999 and 2012, we initially retrieved 220,082 patients who had already experienced their first episode of sepsis. Table 1 summarized the etiology, case numbers, and percentage of sepsis and acute organ dysfunction. A total of 134,444 patients (134,444 of 220,082, 61.09%) had survived to discharge and were included in the study. After a propensity score matching ratio of 1:5, we retrieved 7356 patients for the study cohort, and another 36,780 as the comparison cohort.

Table 2 summarized the demographic characteristics, income, level of urbanization, Charlson Comorbidity Index score (CCI score), baseline comorbidities, and medications between the two cohorts after propensity score matching. The study and comparison cohorts had a mean (median) follow-up period of 3.83 (3.12) years and 3.26 (2.05) years, respectively.

During the follow-up period, the incidences of mortality in the study and comparison cohorts were 0.1 and 0.29 per 1000 person-days, respectively. In the univariate analysis of the Cox regression model, the crude HR was 0.32 (95% CI 0.3–0.34) for the use of statins. After adjusting for the use of statins (defined as >30 cDDDs), age, gender, income, level of urbanization, and baseline comorbidities in the further multivariate analysis, the study cohort had an adjusted HR of 0.29 (0.27–0.31) for long-term mortality by referring to the comparison cohort.

Table 1

Etiology of sepsis and acute organ dysfunction in patients who had experienced their first episode of sepsis.

Variables (*n*=220,082)	*n*	%
Etiology of sepsis		
Central nervous system infection	1382	0.63
Respiratory system infection	87,748	39.87
Cardiovascular system infection	1614	0.73
Gastrointestinal system infection	17,812	8.09
Genitourinary system infection	66,518	30.22
Soft tissue/Musculoskeletal system infection	10,960	4.98
Primary bacteremia	220,082	100.00
Device-related infection	3712	1.69
Others/Undetermined infection (including tuberculosis)	17,651	8.02
Acute organ dysfunction		
Cardiovascular	70,161	31.88
Respiratory	82,001	37.26
Renal	29,835	13.56
Hepatic	6980	3.17
Neurologic	7062	3.21
Hematologic	5122	2.33
Metabolic	2860	1.30

Table 2

Demographic characteristics of the study and comparison cohorts composed of propensity score-matched patients who had survived their first episode of sepsis.

	Nonusers of statin or users with <30 cDDDs (n=36,780)		Statin users >30 cDDDs (n=7356)		
Variables	**n**	**%**	**n**	**%**	**Standardized mean difference**
Gender					
Female	19,317	52.52	3822	51.96	0.011
Male	17,463	47.48	3534	48.04	0.011
Age group, years					
18–40 years	2097	5.7	201	2.73	0.148
40–60 years	9119	24.79	1,927	26.2	0.032
60–80 years	16,993	46.2	3,987	54.2	0.16
>80 years	8571	23.3	1,241	16.87	0.161
Mean (SD)	67.39 (15.43)		67.27 (13.05)		0.008
Insurance premium (NT dollars)					
<20,000	19,632	53.38	3795	51.59	0.036
20,000–40,000	13,793	37.50	2940	39.97	0.051
40,000–60,000	2,448	6.66	480	6.53	0.005
>60,000	907	2.47	141	1.92	0.038
Level of urbanization					
1 (highest)	9339	25.39	1964	26.7	0.03
2	10,631	28.9	2105	28.62	0.006
3	5650	15.36	1133	15.4	0.001
4	5786	15.73	1116	15.17	0.015
5 (lowest)	5374	14.61	1038	14.11	0.014
CCI score					
0	930	2.53	93	1.26	0.093
1	2100	5.71	477	6.48	0.032
2	2109	5.73	534	7.26	0.062
3	2165	5.89	556	7.56	0.067
>4	29,476	80.14	5696	77.43	0.066
Baseline comorbidities					
HTN	28,435	77.31	5666	77.03	0.007
Hyperlipidemia	24,574	66.81	4892	66.50	0.007
CHF	9478	25.77	1812	24.63	0.026
COPD	15,963	43.40	3094	42.06	0.027
CLD	12,619	34.31	2452	33.33	0.021
CKD	14,087	38.30	2787	37.89	0.009
IHD	17,634	47.94	3444	46.82	0.023
Cancer	8158	22.18	1630	22.16	0.001
DM	27,459	74.66	5461	74.24	0.01
Drugs					
Aspirin	4688	12.75	1043	14.18	0.042
NSAID	26,476	71.98	5473	74.4	0.055
Steroid	15,856	43.11	2278	30.97	0.253
Immunosuppressants	138	0.38	67	0.91	0.067

CCI = Charlson comorbidity index, CHF = congestive heart failure, CKD = chronic kidney disease, CLD = chronic liver disease, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, HTN = hypertension, ICU = intensive care unit, IHD = ischemic heart disease, NSAID = nonsteroid anti-inflammatory drug.

Within the study cohort, for the users of statins with cDDDs of 30–180, 180–365, and >365 during the follow-up period, the adjusted HRs for long-term mortality were 0.32 (95% CI, 0.30–0.34), 0.22 (95% CI, 0.19–0.26), and 0.16 (95% CI, 0.12–0.23), respectively, and were presented in a dose–response manner (P for trend <.0001) (Fig. 1). In the Kaplan–Meier analysis, we found a better long-term survival rate in the study cohort with a log-rank test of P<.0001 (Fig. 2A). In the stratification analysis according to the cumulative dose of statins, the Kaplan–Meier analysis also showed an increased long-term survival rate in the groups of high-dose users (log-rank test of P<.0001) (Fig. 2B). Logistic regression model was performed for gastrointestinal bleeding and MACEs in statin and non-statin users. Statin use of >30 cDDDs had significant effect (P<.0001) for gastrointestinal bleeding, ischemic stroke, and acute myocardial infarction in patients who had survived their first sepsis. The results showed in Table 3.

Table 4 showed the stratification analyses by age, gender, income, level of urbanization, CCI score, use of inotropic agents, ICU admission, and receiving mechanical ventilation (the latter three procedures were conducted during the index hospitalization). All the subgroups showed that the use of statins was associated with a decreased adjusted HR for mortality. Furthermore, the use of statins resulted in a more decreased adjusted HR in the groups having a CCI score >4, used inotropic agents, ICU admission, mechanical ventilation, and who were the populations of patients with poor clinical prognostics.

In the sensitivity analysis, we further excluded the fragile patients who had died soon after post-sepsis discharge. That is, we excluded the patients who died between 3 and 6 months after post-sepsis

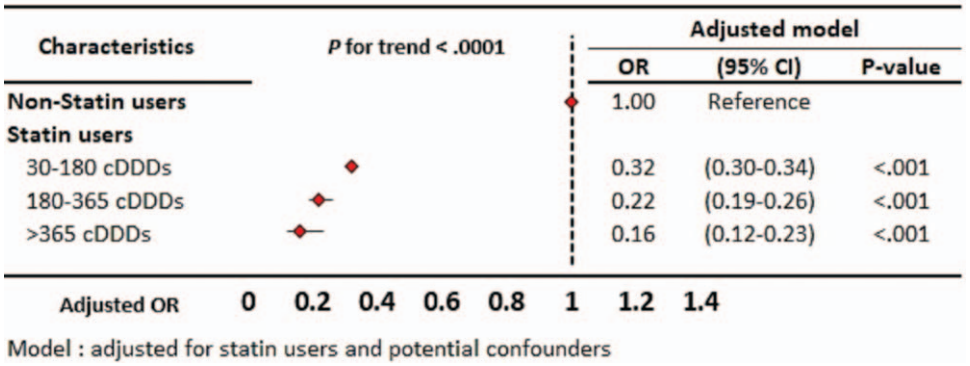

Figure 1. The forest plot showed the adjusted HRs of three groups of users: cumulative Defined Daily Doses (cDDDs) of 30–180, 180–365, and >365, compared with the comparison cohort of nonuser or the use of statins <30 cDDDs.

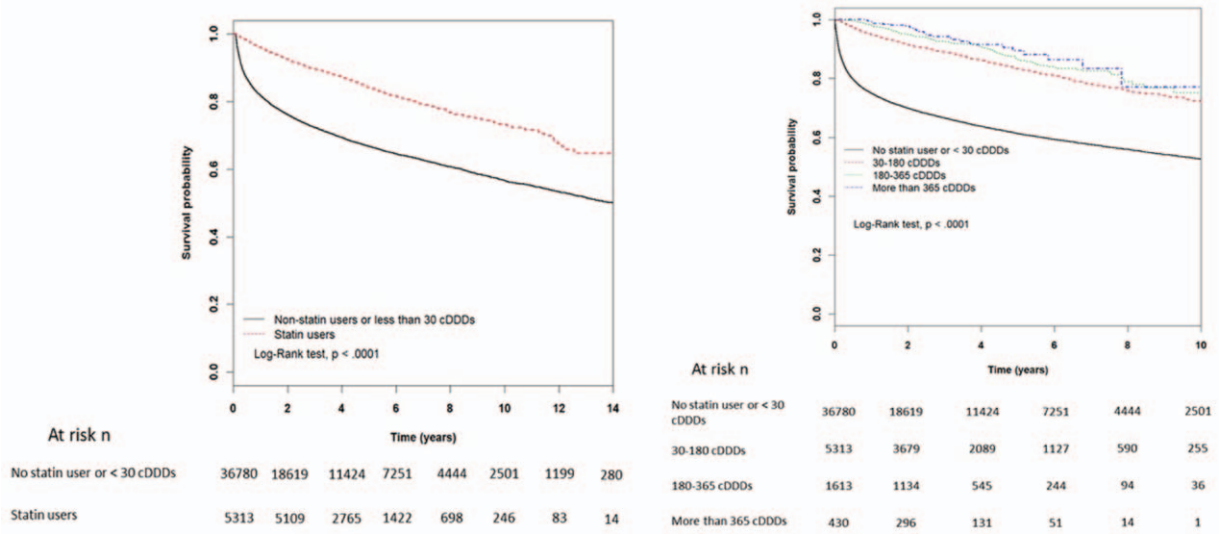

Figure 2. The Kaplan–Meier analysis with the log-rank test showed a better long-term survival rate in the study cohort (A). In the stratification analysis, according to the cumulative Defined Daily Doses (cDDDs), the Kaplan–Meier analysis with the log-rank test showed a better long-term survival rate in the users of a higher statin cumulative dose (B).

discharge from the index hospitalization of sepsis. Both the adjusted HRs remained significant (adjusted HR = 0.35, 95% CI 0.32–0.37 and adjusted HR = 0.42, 95% CI 0.39–0.45) for mortality (Supplement Table 1, http://links.lww.com/MD/C945).

4. Discussion

Sepsis would disrupt the balance between endothelial nitric oxide synthase (eNOS), which is essential for adequate endothelial function, and inducible nitric oxide synthase. Statins could express eNOS. Simvastatin had been proved to be effective in hemodynamic stabilization, improved responses to beta-adrenergic vasopressin drugs, increasing blood pressure, and decreased adhesion of polynuclear cells to the previously activated endothelium in animal study.[10,11,16] Although a meta-analysis based on 9 prospective randomized trials had concluded that statin could not improve mortality in septic patients compared with placebo-controls,[17] a meta-analysis of 27 observational

Table 3

Logistic regression model for gastrointestinal bleeding and major cardiovascular events in statin and non-statin users.

	Statin vs. nonstatin users					
	Crude			Adjusted		
Events (During hospitalization)	OR	(95% CI)	*P*-value	OR	(95% CI)	*P*-value
Gastrointestinal bleeding	0.77	(0.70–0.83)	<.0001	0.81	(0.75–0.89)	<.0001
Ischemic stroke	1.67	(1.51–1.84)	<.0001	1.71	(1.55–1.88)	<.0001
Acute myocardial infarction	2.95	(2.72–3.20)	<.0001	3.06	(2.81–3.32)	<.0001

95% CI = 95% confidence interval, OR = odd's ratio.
Adjusted OR: adjusted for sex, age, insurance premium, urbanization level, and Charlson comorbidity index score in Logistic regression model.
Reference group was nonstatin users.

Table 4

Stratification analyses by age, gender, income, urbanization level, CCI score, use of inotropic agents, ICU admission, and receiving mechanical ventilation.

	Statin use						Compared with nonusers of statins or <30 cDDD users	
	Nonuser of statins or <30 cDDDs (n=36,780)			Statins users >30 cDDDs (n=7356)				
Variables	Event	Person days	IR†	Event	Person days	IR†	Crude HR (95% CI)	Adjusted HR (95% CI)
Total	12,884	43,841,716	0.29	981	10,296,368	0.1	0.32 (0.3–0.34)***	0.29 (0.27–0.31)***
Gender								
Female	6214	24,657,585	0.25	448	5,607,037	0.08	0.31 (0.28–0.34)***	0.3 (0.27–0.33)***
Male	6670	19,184,131	0.35	533	4,689,331	0.11	0.32 (0.29–0.35)***	0.28 (0.26–0.31)***
Age group, years								
18–40 years	297	4321,393	0.07	17	358,829	0.05	0.62 (0.38–1.01)	0.49 (0.3–0.81)**
40–60 years	2186	15,041,306	0.15	146	3,167,089	0.05	0.29 (0.25–0.35)***	0.29 (0.24–0.34)***
60–80 years	6309	19,400,649	0.33	548	5,529,448	0.10	0.31 (0.28–0.33)***	0.28 (0.26–0.31)***
>80 years	4092	5,078,368	0.81	270	1,241,002	0.22	0.3 (0.27–0.34)***	0.29 (0.26–0.33)***
Insurance premium (NT dollars)								
<20,000	8170	19,745,100	0.41	595	5,221,662	0.11	0.28 (0.26–0.31)***	0.27 (0.25–0.3)***
20,000–40,000	3948	18,696,366	0.21	339	4,175,637	0.08	0.36 (0.32–0.4)***	0.33 (0.29–0.36)***
40,000–60,000	547	3,985,309	0.14	33	699,580	0.05	0.29 (0.2–0.41)***	0.26 (0.18–0.37)***
>60,000	219	1,414,941	0.15	14	199,489	0.07	0.39 (0.23–0.67)***	0.35 (0.2–0.6)***
Level of urbanization								
1 (highest)	3243	11,488,076	0.28	266	2,778,328	0.10	0.33 (0.29–0.37)***	0.3 (0.26–0.34)***
2	3639	13,084,938	0.28	255	2,955,044	0.09	0.3 (0.26–0.34)***	0.27 (0.24–0.3)***
3	1960	6,728,682	0.29	149	1,624,333	0.09	0.31 (0.26–0.37)***	0.28 (0.24–0.33)***
4	2084	6,514,345	0.32	142	1,563,331	0.09	0.28 (0.24–0.34)***	0.26 (0.22–0.31)***
5 (lowest)	1958	6,025,675	0.32	169	1,375,332	0.12	0.37 (0.31–0.43)***	0.35 (0.3–0.41)***
CCI score								
0	135	2,780,099	0.05	11	207,041	0.05	1.04 (0.56–1.93)	0.82 (0.44–1.53)
1	321	4,924,805	0.07	32	898,760	0.04	0.55 (0.38–0.79)**	0.49 (0.34–0.71)***
2	465	4,036,526	0.12	57	957,257	0.06	0.51 (0.38–0.67)***	0.46 (0.35–0.61)***
3	528	3,404,285	0.16	57	914,056	0.06	0.39 (0.3–0.52)***	0.4 (0.3–0.52)***
>4	11435	28,696,001	0.40	824	7,31,254	0.11	0.29 (0.27–0.31)***	0.27 (0.25–0.29)***
Use of inotropic agents (During hospitalization)								
No	7290	35,209,544	0.21	762	8,366,867	0.09	0.42 (0.39–0.45)***	0.36 (0.34–0.39)***
Yes	5594	8,632,172	0.65	219	1,929,501	0.11	0.2 (0.17–0.23)***	0.2 (0.17–0.22)***
ICU admission (During hospitalization)								
No	6091	30,259,530	0.20	607	7,151,932	0.08	0.39 (0.36–0.43)***	0.34 (0.31–0.37)***
Yes	6793	13,582,186	0.50	374	3,144,436	0.12	0.26 (0.23–0.29)***	0.26 (0.23–0.28)***
Mechanical ventilation (During hospitalization)								
No	9021	39,432,964	0.23	838	9,490,717	0.09	0.37 (0.34–0.39)***	0.32 (0.3–0.35)***
Yes	3863	4,408,752	0.88	143	805,651	0.18	0.24 (0.2–0.28)***	0.25 (0.21–0.3)***

CCI = Charlson comorbidity index, cDDDs = cumulative Defined Daily Doses, CHF = congestive heart failure, CI = confidence interval, CKD = chronic kidney disease, CLD = chronic liver disease, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, HR = hazard ratio, HTN = hypertension, ICU = intensive care unit, IHD = ischemic heart disease, IR = incidence rates, NSAID = non-steroid anti-inflammatory drug.

Adjusted HR: adjusted for the use of statins (defined as use >30 cDDD), age, gender, insurance premium, level of urbanization, comorbidities (including HTN, hyperlipidemia, CHF, COPD, CLD, CKD, IHD, cancer, and DM), and other drug use (aspirin, NSAID, steroid, and immunosuppressants) in the Cox proportional hazards regression.

† per 1000 person-days; * $P < .05$.

** $P < .01$.

*** $P < .001$.

studies concluded that statin treatment could reduce mortality by 35% in patients of sepsis.[14] In this current cohort study, we concluded that the use of statins after post-sepsis discharge improved the long-term prognosis of patients who had survived sepsis. And we further discovered that the use of statins may be of more benefit in the populations of patients who had poor clinical prognostics; that is, the patients with multiple comorbidities (CCI score >4 in this current study), and a higher severity of sepsis during their hospitalization (use of inotropic agents, ICU admission, and receiving mechanical ventilation). Statins significantly reduced the development of sepsis and infection-related organ dysfunction in hospitalized older Chinese patients, but did not reduce 30-day mortality, ICU admission incidence, or length of hospital stay.[18] According to the results by Lee et al, preadmission simvastatin, atorvastatin, and rosuvastatin were associate with a decreased 30-day mortality of 28%, 22%, and 13% compared with nonstatin users, respectively, in patients of sepsis.[14] This nation-scale cohort study skipped the previous non-resolved controversy, "effect of statins prior to or during the course of sepsis and the associated hospital outcomes", and thus provided a new perspective program in post-sepsis care.

4.1. Major cardiovascular events

The case-crossover study by Bohme et al, demonstrated that the risk of ischemic stroke and intracranial hemorrhage remarkably

increased during post-sepsis hospitalization, and that risk increased as the time window narrowed down to the event of sepsis; this relation persisted for up to a 1-year period.[19] A similar result was also demonstrated by Ou et al and Yende et al which further included myocardial infarction, heart failure, and sudden cardiac death as the study endpoints.[6,20] A longitudinal cohort study with a follow-up period of more than 6 years conducted by Wang et al demonstrated that patients of sepsis were at an increased risk of mortality post-sepsis events, and that approximately 70% of the post-sepsis deaths were caused by cardiovascular or pulmonary diseases.[21] These previous studies supported our original hypothesis that there was a markedly increased risk of all types of cardiovascular diseases with subsequent mortality in patients who had survived sepsis, and that the use of statins may reduce the risk factors and therefore increase the long-term survival in patients who had survived sepsis.

The study by Bohme et al, demonstrated that the younger post-sepsis patients were at a higher risk of ischemic stroke compared with the older patients. Our study also showed a better protective effect of statins in the older populations (>40 years) (adjusted HR = 0.29 [95% CI 0.25–0.33]) than in the younger population (18–40 years) (adjusted HR = 0.49 [95% CI 0.3–0.81]). This might be explained by the multietiology of post-sepsis strokes in the younger population, rather than baseline comorbidity burdens, such as atherosclerosis, which are associated with increased age.

4.2. Antimicrobial effects

Preadmission simvastatin was found to reduce mortality of sepsis through preservation of cardiac function, attenuation of inflammatory cytokines, attenuation of neutrophil infiltration in the lung, and inhibiting T-cell dysfunction in animal studies.[10,11,14] Recently, specific statins were also associated with direct antimicrobial and antivirulence effects.[22] Recurrence and a new-onset of infection were crucial issues in post-sepsis survivors. It still remained a controversy whether statin therapy was associated with a better outcome during the hospitalization of sepsis patients. The meta-analysis performed by Wan et al found that in randomized controlled trials, the use of statins did not significantly decrease the hospital mortality rate during the hospitalization of sepsis patients; however, the observational studies demonstrated that the use of statins was associated with a significant decrease in hospital mortality.[12] In the above-mentioned clinical trials, statins of interest were usually *de novo*, prescribed to the study populations during their hospitalization for sepsis, with the placebo users regarded as the comparison cohort. However, in observational studies, the users of statins were usually pretreated patients who had used statins and were further compared with the nonstatin users. A national cohort study by Caffrey et al, demonstrated that amongst the patients with *Staphylococcus aureus* bacteremia, the continuation of statin therapy among the pretreated patients who had used statins was associated with a significant beneficial effect on 30-day hospital mortality, but not in *de novo* statin-users or in patients who had used statins without the continuation of statin therapy after admission.[23] From these studies, it was reasonable to infer that statin therapy should continue for a period up to achieving an effective cumulative dose, in order to exert its protective effects in patients of sepsis. This is relatively consistent with our study in that the protective effect of statins was positively proportional to the cDDDs.

Statins could suppress adhesion molecules, both in monocytes/neutrophils and endothelial cells, with a result of decrease in the migration of polynuclear neutrophils to tissues.[10,11,16] Prior studies had demonstrated the effect of statins towards the prevention of infections, and their ability to reduce the severity of sepsis via their immunomodulatory and anti-inflammatory effects.[22] Masadeh et al demonstrated the antibacterial activity between atorvastatin, simvastatin, and rosuvastatin.[24] McDowell et al reported that simvastatin was protective during incidences of *Staphylococcus aureus* pneumonia.[25] The study by Su et al, reported that the use of statins was associated with a lower risk of *Mycobacterium tuberculosis* infection.[13] Liappis et al demonstrated the protective effects of statins on mortality in patients of bacteremia, not only for *Staphylococcus aureus* but also in aerobic gram-negative bacilli bacteremia.[26] Basic laboratory studies have also demonstrated similar results to the clinical studies regarding the antimicrobial effect of statins. Statt et al reported that statins could enhance cellular resistance against bacterial pore-forming toxins in airway epithelial cells.[27] The study by Graziano et al, also showed that simvastatin could be used as a potential drug against *Staphylococcus aureus* biofilm.[28] These studies might support our second hypothesis that the use of statins improved the long-term post-sepsis outcome due to its potential antibacterial effects, therefore reducing recurrent infections.

4.3. Healthy user bias

"Healthy user bias" is frequently proposed as being a powerful source of unmeasured confounding in the retrospective study of "statins in adverse outcomes of sepsis ". It is described as a higher health awareness and healthier lifestyle in patients of statin-users, compared with nonstatin users.[14,17,29] According to this theory, statin-users are more likely to seek out preventive healthcare services, such as screening tests and vaccinations.[29,30] However, it is quite difficult to measure the factors involving lifestyle, prevention behavior toward disease, and compliance of drugs in observational studies. The differences between randomized trial and observational study could be explained by healthy user bias, the specific type of statin, timing of statin treatment, and severity of patient population.[14] To reduce the impact of confounding resulting from the "healthy user bias", we used the individual insurance premium as a proxy to adjust for socioeconomic status. Additionally, we considered the propensity score matching which included the baseline comorbidities, income, and level of urbanization as variables, in order to reduce the selection bias related to the "healthy user bias". This statistical methodology also helped the observational studies which were simulating the randomized control trials.

4.4. Indication bias of statins

The indication bias of statin may also be challenged in this study. In Taiwan, statins are not available over the counter. The physicians' decision on prescribing statin therapy should not only follow the treatment guidelines for the specific disease, but also the payment regulations by the NHIA (Supplement Table 2, http://links.lww.com/MD/C945). If the prescriptions were found to be against the rules, the NHIA could not only refuse to pay the medical fee, but may also punish the physicians with a maximal 100-fold rebound (because the national health insurance program is a single-payer, compulsive insurance coverage policy

in Taiwan, the NHIA has the full authority to control all medical facilities and healthcare professionals).

4.5. Strengths

Our study displayed several strengths. First, this nation-scale study provided a large sample size and a longer observation time as mentioned in the title, as we stated "long-term" rather than a short interval of 1 year (or an even shorter period) from admission to discharge. Second, the included patients were categorized into 4 groups according to the cDDDs of statins during the follow-up period (nonusers or users <30 cDDDs, users of 30–180, 180–365, and >365 cDDDs). These categorizations helped better examine the possible dose–response effect in this current observational study. Third, we conducted sensitivity analyses, which excluded the patients who had survived discharge after their first episode of sepsis, but died between 3 and 6 months after post-sepsis discharge. Most surviving sepsis patients died not long after discharge due to multiple factors. From the sensitivity analyses, we were able to further examine the long-term protective effect of statins.

4.6. Limitations

Because of the limitations of our database, we could not further verify if the surviving sepsis patients would have had a lower incidence rate of MACEs and infections. However, this study remains to be of importance, as it serves as a good beginning for future research. Second, we did not have access to the clinical and laboratory data of the enrolled sepsis patients, including body mass index (BMI), waist circumference, blood pressure (systolic and diastolic), exercise, smokers, alcohol intake, metabolic syndrome, lipids, lipids ratio, high-sensitivity C-reactive protein, fasting glucose, culture report, and family history of stroke, coronary artery disease, and peripheral artery disease; that being the serial lipid profiles and BMI data which may change over time. However, in the real world, this data remains difficult to collect once the follow-up time has become longer. Third, this work shares the universal limitations of all studies taken from databases, in that the drug dispensing or prescribing are not always the patient's actual drug intake. Fourth, we did not have access to the final information regarding the mortality causes of the enrolled patients, such as adverse MACEs and recurrent infections.

4.7. Future directions

Randomized control trial for the mechanisms and post-sepsis dose–response effect of different statins to prove the protective effect of MACEs and recurrent infections in patients who have survived sepsis will be the further research. Collect the clinical, laboratory data, and biomarkers (such as interleukin-1β, interleukin-6, and tumor necrosis factor-α) to examine the association between those and doses of different statins.

5. Conclusions

The use of satins may have the potential to improve the long-term outcomes of patients who have previously survived sepsis via their complex mechanisms, particularly in the populations of patients who had poor clinical prognostics, such as multiple comorbidities and a higher severity of sepsis during hospitalization. Although, additional evidence, including clinical and laboratory data, is still needed in order to confirm this observation, this conclusion provides a new perspective program in post-sepsis care.

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