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ORIGINAL ARTICLE

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Use of Statin During Hospitalization Improves the Outcome After Intracerebral Hemorrhage

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SUMMARY

Aims: To examine the relationship between statin use in Chinese patients with intracerebral hemorrhage (ICH) during their hospitalization and the outcomes. **Methods:** Data were collected from the China National Stroke Registry. Good functional outcome was defined by a modified Rankin Scale score between 0–2. Functional outcome and rate of mortality at 3 months and 1 year were compared between ICH patients on statin and those without it during their hospitalization. Odds ratios (ORs) with 95% confidence intervals (CI) were calculated using the multivariable logistic regression model adjusted for baseline risk factors. **Results:** Among 3218 consecutive ICH patients from 2007 to 2008, 220 (6.8%) were on statin during their hospitalization. Compared with those without statin, patients on statin were younger, had more stroke risk factors but lower stroke severity. ICH patients on statin had better functional outcome at 3 months (OR 2.24, 95% CI 1.49–3.36) and at 1 year (OR 2.04, 95% CI 1.37–3.06). They also had lower rate of mortality at 3 months (OR 0.44, 95% CI 0.22–0.87) and 1 year (OR 0.49, 95% CI 0.27–0.86). **Conclusions:** In-hospital statin use in ICH patients is associated with better functional outcome and lower mortality at 3 months and 1 year.

Introduction

Spontaneous intracerebral hemorrhage (ICH) causes about 15% of all strokes in Western populations but 20–30% of strokes in Chinese population [1–4]. Patients with ICH generally have a poorer prognosis and higher case fatality rate compared with those with ischemic strokes [1,5]. Statins are 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors. Even though they are primarily used as cholesterol lowering agents, they also possess potential neuronal protective effects in ICH. Such benefit has been reported in several animal studies [6–8]. However, this benefit is inconclusive in human [9–18]. Several studies suggested that prior [9,11,12,14] or continued [16,17] statin use by ICH patients has improved their functional outcome, but others reported no significant change [10,13,15,18]. Some even suggested that there is an independent association of statin to higher risks of developing ICH [19]. Therefore, the use of statin therapy after ICH remains controversial [20–23].

Using the data from the China National Stroke Registry (CNSR) [4], we examined the relationship between statin treatment in ICH patients during their hospitalization and outcomes.

Methods

Study Design and Population

Data were collected from CNSR [4,5], a nationwide prospective registry of 21,902 consecutive patients with a diagnosis of ischemic stroke, ICH or transient ischemic attack from 132 hospitals in China between September 2007 and August 2008. Data on demographics, vascular risk factors, clinical characteristics, medical therapies and outcomes at the 3-, 6-, 12-month follow-up visits were collected. The collection of data for the CNSR study was approved by ethics committees at all participating hospitals. All patients or his/her legal representatives gave written informed consent before being entered into the registry.

ICH was diagnosed according to the World Health Organization criteria [24] and confirmed by brain computerized tomography (CT). ICH patients older than 18 and presented to hospital within 14 days after the onset of symptoms were eligible for this study. Patients were excluded if they had any one of these conditions: ICH caused by brain tumor, data on ICH hematoma volume were unavailable, primary intraventricular hemorrhage, their prestroke modified Rankin Scale (mRS) was >2, and those did not give consents or lost to follow-up. We also excluded patients with history of prestroke use of lipid lowering agents to avoid its impact on the outcome for the current analysis [9,11,12]. Details on the design, rationale and methodology of CNSR have been published previously [4,5].

Data Collection and Risk Factors Definition

Initial noncontrast CT (NCCT) scans were performed with a section thickness of 9 mm supratentorially and 4.5 mm infratentorially. ICH hematoma volume was measured on the initial NCCT of head using the *ABC*/2 method, in which *A* was the greatest diameter on the largest hemorrhage slice, *B* was the diameter perpendicular to *A*, and *C* was the approximate number of axial slices with hemorrhage multiplied by the slice thickness [5]. Hematoma locations were classified as supratentorial and infratentorial. The presence or the absence of intraventricular extension was also noted on the initial NCCT of head.

Diabetes mellitus was defined as patient had history of diabetes mellitus or was on oral hypoglycemic medication. Hypertension was defined as patient had history of hypertension or was on antihypertensive medication. Dyslipidemia was defined as patient had history of dyslipidemia or was on lipid lowering medication. Atrial fibrillation was defined as patient had history of atrial fibrillation confirmed by at least one electrocardiogram or the presence of the arrhythmia during hospitalization. Serum lipid profile abnormality was defined as such [25]: high total cholesterol level (TC, ≥5.18 mmol/L), high triglycerides level (TG, ≥1.7 mmol/L), low high-density lipoprotein cholesterol level (HDL-C, <1.03 mmol/L in male, <1.30 mmol/L in female), and abnormal low-density lipoprotein cholesterol level (LDL-C, ≥2.59 mmol/L).

Data on whether patients were treated with statin during hospitalization after ICH were recorded. Statin use was defined as there was any documentation of at least one kind of statin use at any time during hospitalization [16]. Statin types included simvastatin, atorvastatin, fluvastatin, pravastatin, and lovastatin, which were prescribed regularly by physicians in China. Patients were divided into two groups: those on statin during hospitalization after ICH and those who were not.

Outcome Measures

At 3 months and 1 year after ICH onset, the outcomes of all patients were assessed by telephone interview. The telephone follow-up was centralized for all patients and a standardized interview protocol was used by all. The primary outcomes included functional outcomes at 3 months and 1 year. Based on previously reported studies [12,13,18], good functional outcome was defined as mRS 0-2 and poor functional outcome was defined as mRS 3-6 (dependency or death). The secondary outcomes included mortality at 3 months and at 1 year.

Statistical Analysis

Categorical variables were presented as percentages and continuous variables as mean±SD or median (Q1-Q3). Differences between the statin group and no statin group were compared using chi-square (χ^2) test for categorical variables, and *t* test or Mann–Whitney *U* test for continuous variables. For each outcome variable, a separate univariable and multivariable logistic regression were performed. Odds ratios (ORs) with 95% confidence intervals (CI) were calculated using the no statin group as the reference. All significant baseline variables in the univariable analysis were included in the multivariable analysis. A propensity score model was developed to improve the sensitivity of analysis. The propensity for statin use during hospitalization was determined regardless of the outcome using a nonparsimonious multivariable logistic regression model. All baseline variables listed in Table 1 were included to calculate the propensity score. A propensity score, indicating the predicted probability of receiving statin treatment, was then calculated from the logistic equation for each patient. The model's reliability and predictive validity were tested with the Hosmer–Lemeshow goodness-of-fit test ($P = 0.719$) and the c-index (c = 0.804). The propensity score was then included along with the comparison variable (no statin or not no statin) in multivariable analyses of outcome producing an adjusted OR with 95% CI. To estimate the effect of early withdrawal of care on our findings, we also performed sensitivity analyses excluding all patients who died within the first 48 h of admission.

The α level of significance was defined as $P < 0.05$. All analyses were performed with SAS software version 9.3 (SAS Institute Inc, Cary, NC, USA).

Results

A total of 3218 ICH patients were eligible for this analysis, with a mean age of 62.1 years, and 38.8% were female. Among them, 220 (6.8%) patients were on statin during hospitalization after ICH. The median length of hospital stay was 18 (11–26) days for overall patients, 19 (13–26) days for patients on statin and 18 (10–26) days for patients not on statin, respectively ($P = 0.16$).

The demographics and clinical characteristics of ICH patients on or without statin during hospitalization after ICH are presented in Table 1. Compared with those not on statin, patients who were on statin during hospitalization were younger, had more risk factors (heavy alcohol use, diabetes mellitus, hypertension, history of dyslipidemia, higher total cholesterol, triglyceride, and low-density lipoprotein cholesterol), had lower stroke severity on presentation (lower NIHSS score, higher Glasgow Coma Scale score, smaller hematoma volume, and less intraventricular extension), were more likely taking antihypertensive agents before or after ICH and antiplatelet agents before ICH, and less likely being treated with intravenous mannitol, NICU/ICU care or withdraw of support.

The proportion of all ICH patients (on statin group and not on statin group) with poor functional outcome was 49.1% at 3 months and 46.0% at 1 year, and the case fatality rate was

Table 1 Baseline characteristics of patients on or not on statin during hospitalization after intracerebral hemorrhage

Characteristics	Total (*N* = 3218)	On statin (*N* = 220)	Not on statin (*N* = 2998)	*P* value
Age (year), mean (SD)	62.1 ± 13.1	60.7 ± 11.9	62.2 ± 13.2	0.003
Female, *n* (%)	1248 (38.8)	85 (38.6)	1163 (38.8)	0.97
Current smoking, *n* (%)	1210 (37.6)	85 (38.6)	1125 (37.5)	0.74
Heavy drink, *n* (%)	363 (11.3)	35 (15.9)	328 (10.9)	0.02
Medical history, *n* (%)				
Diabetes mellitus	271 (8.4)	30 (13.6)	241 (8.0)	0.004
Hypertension	2177 (67.7)	175 (79.6)	2002 (66.8)	<0.001
Dyslipidemia	206 (6.4)	32 (14.6)	174 (5.8)	<0.001
Cardiovascular disease	261 (8.1)	19 (8.6)	242 (8.1)	0.77
Atrial fibrillation	51 (1.6)	5 (2.3)	46 (1.5)	0.57
Stroke	868 (27.0)	67 (30.5)	801 (26.7)	0.23
Dyslipidemia on admission, *n* (%)				
TC ≥ 5.18 mmol/L	691 (21.5)	125 (56.8)	566 (18.9)	<0.001
TG ≥ 1.7 mmol/L	684 (21.3)	99 (45.0)	585 (19.5)	<0.001
HDL-C < 1.03 mmol/L (Male), <1.3 mmol/L (Female)	862 (26.8)	54 (24.6)	808 (27.0)	0.44
LDL-C ≥ 2.59 mmol/L	1323 (41.1)	162 (73.6)	1161 (38.7)	<0.001
Stroke severity, median (IQR)				
NIHSS score on admission	9 (3–17)	5 (2–10)	9 (3–17)	<0.001
GCS score on admission	14 (9–15)	15 (13–15)	14 (8–15)	<0.001
Hematoma volume (mL)	12.7 (5.6–28.1)	8.1 (4.0–16.8)	13.5 (5.8–30.0)	<0.001
Supratentorial, *n* (%)				
≤30 mL	2341 (82.7)	174 (91.1)	2167 (82.1)	0.006
30–60 mL	286 (10.1)	11 (5.8)	275 (10.4)	
>60 mL	203 (7.2)	6 (3.1)	197 (7.5)	
Infratentorial, *n* (%)				
≤10 mL	276 (71.1)	22 (75.9)	254 (70.8)	0.38
10–20 mL	60 (15.5)	2 (6.9)	58 (16.2)	
>20 mL	52 (13.4)	5 (17.2)	47 (13.1)	
Hematoma location, *n* (%)				
Supratentorial	2830 (87.9)	191 (86.8)	2639 (88.0)	0.60
Infratentorial	388 (12.1)	29 (13.2)	359 (12.0)	
Intraventricular extension, *n* (%)	952 (29.6)	52 (23.6)	900 (30.0)	0.045
Medication history, *n* (%)				
Antihypertensive	1357 (42.2)	114 (51.8)	1243 (41.5)	0.003
Antiplatelet	267 (8.3)	26 (11.8)	241 (8.0)	0.049
Anticoagulants	30 (0.9)	5 (2.3)	25 (0.8)	0.08
Treated in, *n* (%)				
Neurology ward/Ward	1995 (62.0)	149 (67.7)	1846 (61.6)	<0.001
Stroke unit	548 (17.0)	54 (24.6)	494 (16.5)	
Neurosurgical/Intervention Ward	94 (2.9)	4 (1.8)	90 (3.0)	
NICU/ICU	581 (18.1)	13 (5.9)	568 (18.9)	
Medical treatment during hospitalization, *n* (%)				
Antihypertensive therapy	1888 (58.7)	168 (76.4)	1720 (57.4)	<0.001
Intravenous mannitol	2769 (92.9)	193 (88.1)	2576 (93.2)	0.005
Neurosurgical intervention	81 (2.7)	2 (0.9)	79 (2.9)	0.09
Withdraw of support, *n* (%)	400 (12.4)	12 (5.5)	388 (12.9)	0.001

SD, standard deviation; IQR, interquartile range; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale.
P values indicate comparison of on statin group with not on statin group (Pearson chi-square test for categorical and *t* test or Mann–Whitney *U* test for continuous variables).

20.0% at 3 months and 26.0% at 1 year, respectively. Distribution of mRS scores at 3 months and 1 year in each group is shown in Figure 1. Baseline characteristics of patients after intracerebral hemorrhage for 3-month and 1-year functional outcomes and mortalities are shown in Tables 2 and 3, respectively. Multivariable logistic regression adjusted for potential confounding variables in the entire cohort revealed that statin use during hospitalization was associated with more than twofold odds of having a good functional outcome at 3 months (adjusted OR 2.24, 95% CI 1.49–3.36, $P < 0.001$) and 1 year (adjusted OR 2.04, 95%

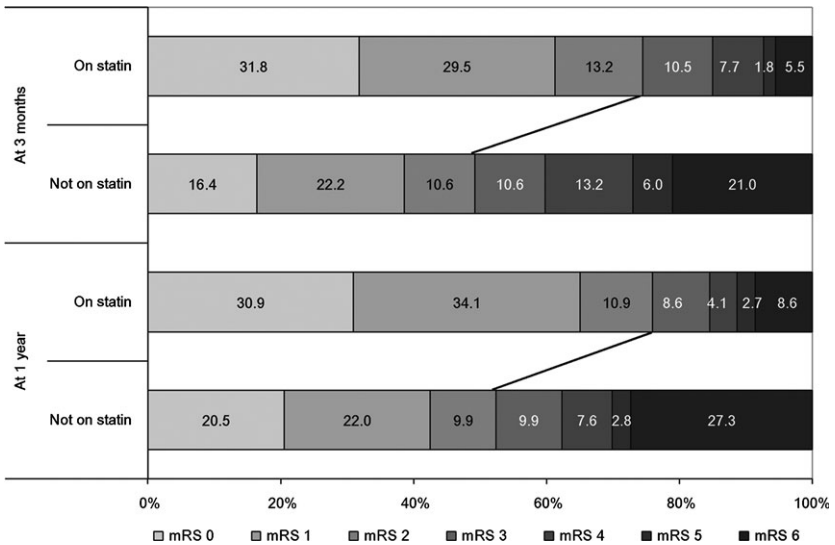

Figure 1 Distribution of modified Rankin Scale (mRS) scores at 3 months and 1 year by groups. The size of the bars indicates the percentage of patients with a particular mRS score in groups of patients with or without statin use during hospitalization.

CI 1.37–3.06, $P < 0.001$), and greater than 50% lower mortality rate at 3 months (adjusted OR 0.44, 95% CI 0.22–0.87, $P = 0.02$) and 1 year (adjusted OR 0.49, 95% CI 0.27–0.86, $P = 0.01$). These results were confirmed in models adjusted for propensity score in the entire cohort and in models that exclude death within the first 48 h of admission (Table 4).

Discussion

In this retrospective analysis of prospectively collected multicenter registry data, we found that statin use during hospitalization in patients with acute ICH was associated with favorable functional outcome and lower mortality both at 3 months and 1 year. Our study focused on the effect of statin use during hospitalization, which is different from others that focused on the effect of prior statin use [9–15,18] or discontinuation of statin [16,17]. Our study found that only small percentage of Chinese ICH patients were on statin during hospitalization (6.8%), which is significantly lower than that in Western patients (14–44%) [16,26,27]. Our findings were confirmatory to other published results [16,26,27]. Another study in a smaller cohort showed similar results that in-hospital statin treatment after ICH was associated with decreased odds of death or disability at 12 months [27]. Report from the Registry of the Canadian Stroke Network ($N = 2466$) suggested that ICH patients who were on statin during hospitalization had better functional outcome at discharge. However, such benefit was lost once patients who died within 48 h or discharged to palliative care were excluded [16].

It is possible that starting an ICH patient on statin can be biased in observational study [11,16,28]. It is an evidence of confounding by indication that statin use during hospitalization may have been a marker for those patients who may have more stroke risk factors or lower stroke severity. Physicians prescribed statins in ICH patients for dyslipidemia, not for ICH. Physicians are less likely to prescribe statins in patients with more severe hemorrhagic stroke or in those with dysphagia and unable to swallow medications [16]. If so, statin therapy could indicate less severe stroke. Age and stroke severity variables were independent risk factors of unfavorable prognosis. For instance, the multivariable regression analyses in our study shows younger age (adjusted OR 0.95, 95% CI 0.94–0.96), lower NIHSS score (adjusted OR 0.88, 95% CI 0.86–0.89), higher Glasgow Coma Scale score (adjusted OR 1.07, 95% CI 1.04–1.10), smaller hematoma volume (adjusted OR 0.98, 95% CI 0.98–0.99), and less intraventricular extension (adjusted OR 0.63, 95% CI 0.50–0.78) are associated with good outcome at 1 year. These baseline characteristics of patients on statin could indicate favorable prognosis. We performed multivariable regression analysis adjusted for baseline variables or the propensity score and sensitivity analyses after excluding death within the first 48 h of admission. The consistency of these analyses emphasized the robustness of the results.

Our study has several limitations. First, the CNSR study is a prospective registry study, and the exact dose, starting date, duration, and type of statins used were unavailable. We used the definition of statin use during hospitalization according to another previous study [16] to compare the results with each other. It is noted that high-dose statin therapy may be associated with a higher risk of ICH [19]. However, this association is not significant in a recent meta-analysis of 31 randomized controlled trials [29]. A retrospective cohort study including 17872 ischemic stroke patients found no dose–response association between statin use and ICH, and also no interaction between statin therapy and subgroup characteristics including age and gender [30]. Secondary brain injury takes place soon after the ICH, and acute inflammatory reaction lasts for a few weeks after ICH in animal models [31–33]. Starting statin therapy at different stages of brain injury after ICH onset (in the hyperacute phase or 1 week after ICH) may result in different effect of

Table 2 Baseline characteristics of patients after intracerebral hemorrhage for 3-month and 1-year functional outcomes

	3-month outcome[a]			1-year outcome[a]		
Characteristics	Good (*N* = 1638)	Poor (*N* = 1580)	*P* value	Good (*N* = 1736)	Poor (*N* = 1482)	*P* value
Age (year), mean (SD)	59.7 ± 12.5	64.5 ± 13.3	<0.001	59.2 ± 12.2	65.4 ± 13.3	<0.001
Female, *n* (%)	590 (36.0)	658 (41.6)	0.001	642 (37.0)	606 (40.9)	0.02
Current smoking, *n* (%)	648 (39.6)	562 (35.6)	0.02	684 (39.4)	526 (35.5)	0.02
Heavy drink, *n* (%)	206 (12.6)	157 (9.9)	0.02	221 (12.7)	142 (9.6)	0.005
Medical history, *n* (%)						
Diabetes mellitus	118 (7.2)	153 (9.7)	0.01	124 (7.1)	147 (9.9)	0.005
Hypertension	1103 (67.3)	1074 (68.0)	0.70	1172 (67.5)	1005 (67.8)	0.86
Dyslipidemia	123 (7.5)	83 (5.3)	0.009	130 (7.5)	76 (5.1)	0.006
Cardiovascular disease	109 (6.7)	152 (9.6)	0.002	117 (6.7)	144 (9.7)	0.002
Atrial fibrillation	17 (1.0)	34 (2.2)	0.01	19 (1.1)	32 (2.2)	0.02
Stroke	370 (22.6)	498 (31.5)	<0.001	369 (21.3)	499 (33.7)	<0.001
Dyslipidemia on admission, *n* (%)						
TC ≥ 5.18 mmol/L	369 (22.5)	322 (20.4)	0.14	395 (22.8)	296 (20.0)	0.056
TG ≥ 1.7 mmol/L	418 (25.5)	266 (16.8)	<0.001	443 (25.5)	241 (16.3)	<0.001
HDL-C < 1.03 mmol/L (Male), <1.3 mmol/L (Female)	415 (25.3)	447 (28.3)	0.058	433 (24.9)	429 (29.0)	0.01
LDL-C ≥ 2.59 mmol/L	733 (44.7)	590 (37.3)	<0.001	781 (45.0)	542 (36.6)	<0.001
Stroke severity, median (IQR)						
NIHSS score on admission	4 (2–9)	15 (9–25)	<0.001	5 (2–10)	15 (8–25)	<0.001
GCS score on admission	15 (14–15)	10 (6–14)	<0.001	15 (14–15)	10 (6–15)	<0.001
Hematoma volume (mL)	9.0 (4.0–18.0)	20.0 (9.0–42.0)	<0.001	9.1 (4.4–18.8)	20.0 (8.4–45.0)	<0.001
Supratentorial, *n* (%)						
≤30 mL	1374 (94.0)	967 (70.6)	<0.001	1452 (93.6)	889 (69.6)	<0.001
30–60 mL	63 (4.3)	223 (16.3)		74 (4.8)	212 (16.6)	
>60 mL	24 (1.6)	179 (13.1)		26 (1.7)	177 (13.8)	
Infratentorial, *n* (%)						
≤10 mL	139 (78.5)	137 (64.9)	0.01	141 (76.6)	135 (66.2)	0.04
10–20 mL	20 (11.3)	40 (19.0)		26 (14.1)	34 (16.7)	
>20 mL	18 (10.2)	34 (16.1)		17 (9.2)	35 (17.2)	
Hematoma location, *n* (%)						
Supratentorial	1461 (89.2)	1369 (86.6)	0.03	1552 (89.4)	1278 (86.2)	0.006
Infratentorial	177 (10.8)	211 (13.4)		184 (10.6)	204 (13.8)	
Intraventricular extension, *n* (%)	313 (19.1)	639 (40.4)	<0.001	342 (19.7)	610 (41.2)	<0.001
Medication history, *n* (%)						
Antihypertensive	693 (42.3)	664 (42.0)	0.87	737 (42.5)	620 (41.8)	0.72
Antiplatelet	128 (7.8)	139 (8.8)	0.31	135 (7.8)	132 (8.9)	0.25
Anticoagulants	14 (0.9)	16 (1.0)	0.64	13 (0.7)	17 (1.1)	0.24
Treated in, *n* (%)						
Neurology ward/Ward	1128 (68.9)	867 (54.9)	<0.001	1151 (66.3)	844 (57.0)	<0.001
Stroke unit	290 (17.7)	258 (16.3)		322 (18.5)	226 (15.2)	
Neurosurgical/Intervention Ward	40 (2.4)	54 (3.4)		48 (2.8)	46 (3.1)	
NICU/ICU	180 (11.0)	401 (25.4)		215 (12.4)	366 (24.7)	
Medical treatment during hospitalization, *n* (%)						
Antihypertensive therapy	1035 (63.2)	853 (54.0)	<0.001	1100 (63.4)	788 (53.2)	<0.001
Intravenous mannitol	1424 (90.1)	1345 (96.0)	<0.001	1521 (90.8)	1248 (95.5)	<0.001
Neurosurgical intervention	21 (1.3)	60 (4.3)	<0.001	28 (1.7)	53 (4.1)	<0.001
Withdraw of support, *n* (%)	108 (6.6)	292 (18.5)	<0.001	115 (6.6)	285 (19.2)	<0.001

SD, standard deviation; IQR, interquartile range; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale. *P* values indicate comparison of good outcome group with poor outcome group (Pearson chi-square test for categorical and *t* test or Mann–Whitney *U* test for continuous variables). [a]Good outcome defined as modified Rankin Scale 0–2.

Table 3 Baseline characteristics of patients after intracerebral hemorrhage for 3-month and 1-year death

	3-month death			1-year death		
Characteristics	Death (*N* = 642)	Survival (*N* = 2576)	*P* value	Death (*N* = 838)	Survival (*N* = 2380)	*P* value
Age (year), mean (SD)	65.7 ± 14.1	61.2 ± 12.7	<0.001	66.0 ± 13.9	60.7 ± 12.5	<0.001
Female, *n* (%)	259 (40.3)	989 (38.4)	0.36	328 (39.1)	920 (38.7)	0.80
Current smoking, *n* (%)	230 (35.8)	980 (38.0)	0.30	303 (36.2)	907 (38.1)	0.32
Heavy drink, *n* (%)	60 (9.3)	303 (11.8)	0.08	72 (8.6)	291 (12.2)	0.004
Medical history, *n* (%)						
Diabetes mellitus	68 (10.6)	203 (7.9)	0.02	89 (10.6)	182 (7.6)	0.008
Hypertension	426 (66.4)	1751 (68.0)	0.43	559 (66.7)	1618 (68.0)	0.50
Dyslipidemia	26 (4.0)	180 (7.0)	0.007	33 (3.9)	173 (7.3)	<0.001
Cardiovascular disease	62 (9.7)	199 (7.7)	0.11	81 (9.7)	180 (7.6)	0.055
Atrial fibrillation	20 (3.1)	31 (1.2)	<0.001	24 (2.9)	27 (1.1)	<0.001
Stroke	214 (33.3)	654 (25.4)	<0.001	296 (35.3)	572 (24.0)	<0.001
Dyslipidemia on admission, *n* (%)						
TC ≥ 5.18 mmol/L	110 (17.1)	581 (22.6)	0.003	143 (17.1)	548 (23.0)	<0.001
TG ≥ 1.7 mmol/L	75 (11.7)	609 (23.6)	<0.001	106 (12.6)	578 (24.3)	<0.001
HDL-C < 1.03 mmol/L (Male), <1.3 mmol/L (Female)	224 (34.9)	638 (24.8)	<0.001	283 (33.8)	579 (24.3)	<0.001
LDL-C ≥ 2.59 mmol/L	169 (26.3)	1154 (44.8)	<0.001	239 (28.5)	1084 (45.5)	<0.001
Stroke severity, median (IQR)						
NIHSS score on admission	21 (11–33)	7 (3–13)	<0.001	19 (10–31)	7 (2–12)	<0.001
GCS score on admission	7 (4–12)	15 (11–15)	<0.001	7 (4–13)	15 (12–15)	<0.001
Hematoma volume (mL)	28.0 (12.0–60.0)	11.5 (4.7–24.0)	<0.001	24.0 (10.0–55.0)	11.2 (4.5–22.6)	<0.001
Supratentorial, *n* (%)						
≤30 mL	297 (55.8)	2044 (88.9)	<0.001	422 (60.2)	1919 (90.1)	<0.001
30–60 mL	106 (19.9)	180 (7.8)		132 (18.8)	154 (7.2)	
>60 mL	129 (24.2)	74 (3.2)		147 (21.0)	56 (2.6)	
Infratentorial, *n* (%)						
≤10 mL	67 (60.9)	209 (75.2)	0.009	85 (62.0)	191 (76.1)	0.01
10–20 mL	20 (18.2)	40 (14.4)		26 (19.0)	34 (13.5)	
>20 mL	23 (20.9)	29 (10.4)		26 (19.0)	26 (10.4)	
Hematoma location, *n* (%)						
Supratentorial	532 (82.9)	2298 (89.2)	<0.001	701 (83.7)	2129 (89.5)	<0.001
Infratentorial	110 (17.1)	278 (10.8)		137 (16.3)	251 (10.5)	
Intraventricular extension, *n* (%)	344 (53.6)	608 (23.6)	<0.001	413 (49.3)	539 (22.6)	<0.001
Medication history, *n* (%)						
Antihypertensive	253 (39.4)	1104 (42.9)	0.11	331 (39.5)	1026 (43.1)	0.07
Anti-platelet	47 (7.3)	220 (8.5)	0.32	63 (7.5)	204 (8.6)	0.34
Anticoagulants	8 (1.2)	22 (0.9)	0.36	11 (1.3)	19 (0.8)	0.18
Treated in, *n* (%)						
Neurology ward/Ward	349 (54.4)	1646 (63.9)	<0.001	464 (55.4)	1531 (64.3)	<0.001
Stroke unit	75 (11.7)	473 (18.4)		107 (12.8)	441 (18.5)	
Neurosurgical/Intervention Ward	22 (3.4)	72 (2.8)		28 (3.3)	66 (2.8)	
NICU/ICU	196 (30.5)	385 (14.9)		239 (28.5)	342 (14.4)	
Medical treatment during hospitalization, *n* (%)						
Antihypertensive therapy	294 (45.8)	1594 (61.9)	<0.001	402 (48.0)	1486 (62.4)	<0.001
Intravenous mannitol	503 (97.7)	2266 (91.9)	<0.001	659 (96.2)	2110 (91.9)	0.001
Neurosurgical intervention	27 (5.2)	54 (2.2)	0.001	32 (4.7)	49 (2.1)	0.004
Withdraw of support, *n* (%)	181 (28.2)	219 (8.5)	<0.001	216 (25.8)	184 (7.7)	<0.001

SD, standard deviation; IQR, interquartile range; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale. *P* values indicate comparison of death group with survival group (Pearson chi-square test for categorical and *t* test or Mann-Whitney U test for continuous variables).

Table 4 Outcomes of patients on or not on statin during hospitalization after intracerebral hemorrhage

Outcome	Model	On statin *n*/*N* (%)	Not on statin *n*/*N* (%)	Odds Ratio[a] (95% CI)	*P* value
At 3 months					
Good outcome[b]	Entire cohort (*N* = 3218)				
	Univariable	164/220 (74.5)	1474/2998 (49.2)	3.03 (2.22–4.14)	<0.001
	Adjusted for risk factors[c]			2.24 (1.49–3.36)	<0.001
	Adjusted for propensity score			1.93 (1.36–2.72)	<0.001
	Excluding death ≤48 h (*N* = 3073)				
	Univariable	164/219 (74.9)	1474/2854 (51.6)	2.79 (2.04–3.82)	<0.001
	Adjusted for risk factors[c]			2.23 (1.48–3.36)	<0.001
	Adjusted for propensity score			1.90 (1.34–2.68)	<0.001
Death	Entire cohort (*N* = 3218)				
	Univariable	12/220 (5.5)	630/2998 (21.0)	0.22 (0.12–0.39)	<0.001
	Adjusted for risk factors[d]			0.44 (0.22–0.87)	0.02
	Adjusted for propensity score			0.53 (0.28–0.97)	0.04
	Excluding death ≤48 h (*N* = 3073)				
	Univariable	11/219 (5.0)	486/2854 (17.0)	0.26 (0.14–0.48)	<0.001
	Adjusted for risk factors[d]			0.43 (0.21–0.88)	0.02
	Adjusted for propensity score			0.54 (0.29–1.03)	0.06
At 1 year					
Good outcome[b]	Entire cohort (*N* = 3218)				
	Univariable	167/220 (75.9)	1569/2998 (52.3)	2.89 (2.09–3.94)	<0.001
	Adjusted for risk factors[c]			2.04 (1.37–3.06)	<0.001
	Adjusted for propensity score			1.93 (1.36–2.74)	<0.001
	Excluding death ≤48 h (*N* = 3073)				
	Univariable	167/219 (76.3)	1569/2854 (55.0)	2.63 (1.91–3.62)	<0.001
	Adjusted for risk factors[c]			2.05 (1.36–3.07)	<0.001
	Adjusted for propensity score			1.90 (1.34–2.70)	<0.001
Death	Entire cohort (*N* = 3218)				
	Univariable	19/220 (8.6)	819/2998 (27.3)	0.25 (0.16–0.41)	<0.001
	Adjusted for risk factors[d]			0.49 (0.27–0.86)	0.01
	Adjusted for propensity score			0.55 (0.34–0.92)	0.02
	Excluding death ≤48 h (*N* = 3073)				
	Univariable	18/219 (8.2)	675/2854 (23.7)	0.29 (0.18–0.47)	<0.001
	Adjusted for risk factors[d]			0.48 (0.27–0.86)	0.01
	Adjusted for propensity score			0.57 (0.34–0.95)	0.03

CI, confidence interval; mRS, modified Rankin Scale.

[a]Odds ratios using the not on statin group as the reference.

[b]Good outcome defined as modified Rankin Scale 0–2.

[c]Risk factors include the following: age, gender, smoking, heavy drink, history of diabetes mellitus, dyslipidemia, cardiovascular disease, atrial fibrillation and stroke, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, National Institutes of Health Stroke Scale score, and Glasgow Coma Scale score on admission, hematoma volume, hematoma location, intraventricular hemorrhagic extension, NICU/ICU care, antihypertensive therapy, intravenous mannitol therapy, neurosurgical intervention, and withdraw of support during hospitalization.

[d]Risk factors include the following: age, heavy drink, history of diabetes mellitus, dyslipidemia, atrial fibrillation and stroke, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, National Institutes of Health Stroke Scale score, and Glasgow Coma Scale score on admission, hematoma volume, hematoma location, intraventricular hemorrhagic extension, NICU/ICU care, antihypertensive therapy, intravenous mannitol therapy, neurosurgical intervention, and withdraw of support during hospitalization.

inflammation inhibition and other potential neuronal protective effects. It is unclear how long the patients who were started on a statin during the acute hospitalization were maintained on the drug, and the possibility of harm with prolonged use in this population cannot be excluded. Actually, 90.9% of included patients arrived to the registry hospital within 24 h after onset of ICH, and the median length of hospital stay was 18 (11–26) days in our study. Second, the information on participating in rehabilitation and medication compliance after discharge was unavailable, which would affect the outcome in these patients. Third, although statistical adjustment was performed with multivariable models, there is concern for residual, unmeasured confounding.

Conclusion

In this large cohort observational study, statin use during hospitalization in patients with acute ICH was associated

with favorable functional outcome and lower mortality both at 3 months and 1 year. Future clinical trials are needed to further confirm such favorable effect of statin in ICH patients.

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Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

The following supplementary material is available for this article:

Data S1. The CNSR investigators.