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Association between statin use during hospitalisation and mortality in patients with intracerebral haemorrhage: a propensity score-matched cohort study

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ABSTRACT

Objectives We examined the relationship between statin use during hospitalisation and mortality in patients with intracerebral haemorrhage (ICH).

Design Retrospective propensity-matched cohort study.

Setting Patients with ICH (≥18 years old) admitted to Beth Israel Deaconess Medical Center (Boston, Massachusetts, USA) from 2001 to 2012 registered in the Medical Information Mart for Intensive Care III database.

Participants 1043 patients with ICH (≥18 years) were evaluated for the relationship between statin use during hospitalisation and mortality.

Interventions Statin use.

Primary and secondary outcome measures The primary outcome was 90-day mortality. We used multivariable Cox regression analyses to calculate the adjusted HR with 95% CI and used propensity score analysis and an inverse probability weighting (IPW) model to ensure the robustness of our findings.

Results We included 1043 patients with ICH (362 and 681 were statins and non-statin users, respectively) between 2001 and 2012. The overall 90-day mortality was 29.8% (311/1043); it was 33.3% (227/681) and 23.2% (84/362) for non-statin and statin users, respectively. After adjusted for potential confounders, we found that statin use was associated with 29% lower of 90-day mortality (HR=0.71, 95% CI 0.52 to 0.97, p<0.05). IPW also demonstrated a significantly lower 90-day mortality in statin users. The HR was 0.69 (95% CI 0.54 to 0.88, p<0.01). The results remain stable in subgroup analyses and propensity score matching.

Conclusion Statin use during hospitalisation may be associated with reduced risk-adjusted mortality in patients with ICH. Further randomised controlled trials are needed to clarify this association.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We examine the effects of statin use during hospitalisation and mortality in patients with intracerebral haemorrhage (ICH) using a relatively large cohort study.
⇒ To reduce bias, we used a propensity score matching and an inverse probability weighting model on an extensive database.
⇒ One fundamental limitation is that we could not identify the specific aetiology of ICH, which led to the failure to conduct a more detailed subgroup analysis of the causes.
⇒ The cause of death is not recorded in the Medical Information Mart for Intensive Care III database, so we cannot conduct a competitive risk analysis.

INTRODUCTION

Intracerebral haemorrhage (ICH) is one of the leading causes of death and disability worldwide, and there are few established interventions to improve neurological outcomes.[1] In the USA, ICH accounts for 15% of all strokes annually[2] and 20%–30% in Asia.[3] The mortality rate remains high, and survival patients tend to leave severe dysfunction.[1] Therefore, ICH brings a heavy economic and pressure burden to patients, caregivers, family members and society. However, effective prevention and treatment strategies are still minimal.

Statins or 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors are commonly used as the primary therapy to reduce low-density lipoprotein cholesterol levels in patients with hyperlipidaemia. The effectiveness of statins in the primary and secondary prevention of ischaemic cardio-cerebrovascular diseases has also been well proved.[4 5] Many studies have demonstrated that statin can reduce primary and secondary cardiovascular events.[6–10] Several studies have also demonstrated that there was an association between statin use and reduced mortality in patients with ICH.[11–13] However, others reported that this relationship did not exist.[14 15] The relationship between statins and ICH mortality is still controversial. Therefore, we performed this relatively large cohort study to explore the relationship between statin use and mortality in patients with ICH.

METHODS

Database source

We enrolled patients with ICH with and without statin exposure from an extensive, freely available database, Medical Information Mart for Intensive Care (MIMIC) III (version 1.4), comprising more than 40 000 patients who stayed in the Beth Israel Deaconess Medical Center (Boston, Massachusetts, USA) from 2001 to 2012.[16 17] PostgreSQL tools V.12.5 was used to extract data from the database. The Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center's institutional review boards approved the study. One author MY obtained approval to exploit the database (certification number 46868266). All reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[18]

Study population

We included patients over 18 years who were diagnosed with ICH for this study. Patients were excluded if they met the following criteria: (1) patients had no data of statin use record; (2) patients were diagnosed with haemorrhage due to brain trauma, brain tumour or meningioma, and bleeding due to vascular abnormalities or arterial aneurysm; (3) for patients who have been admitted repeatedly, only the record of the first admission should be considered, and patients with hospitalisation of fewer than 48 hours should be excluded.

Statin use

Statin use was defined as a record of using statin in 'Medications during hospitalisation' in MIMIC-III.

Covariates

We included the following variables: age, gender, ethnicity, weight, alcohol drinking, smoking status, comorbidities (atrial fibrillation, diabetes, hypertension, chronic obstructive pulmonary disease (COPD), coronary, heart failure, hyperlipidaemia, kidney), laboratory blood results (white blood cell, blood platelet, blood neutrophil, blood lymphocyte, blood monocyte, serum calcium, serum sodium, serum chlorine, serum potassium, blood glucose, serum creatinine, serum urea nitrogen, activated partial thromboplastin time (APTT), prothrombin time (PT)), Glasgow Coma Scale (GCS) score, Sequential Organ Failure Assessment (SOFA) score, location of ICH and statin type. These variables include those that represent patients' health habits using statins so beneficial user effects can be captured.[19]

Outcome

The outcome was 90-day mortality.

Propensity score matching

To minimise the potential bias of treatment allocation and confounding, propensity score matching (PSM)[20] was used to estimate the likelihood that patients were statin

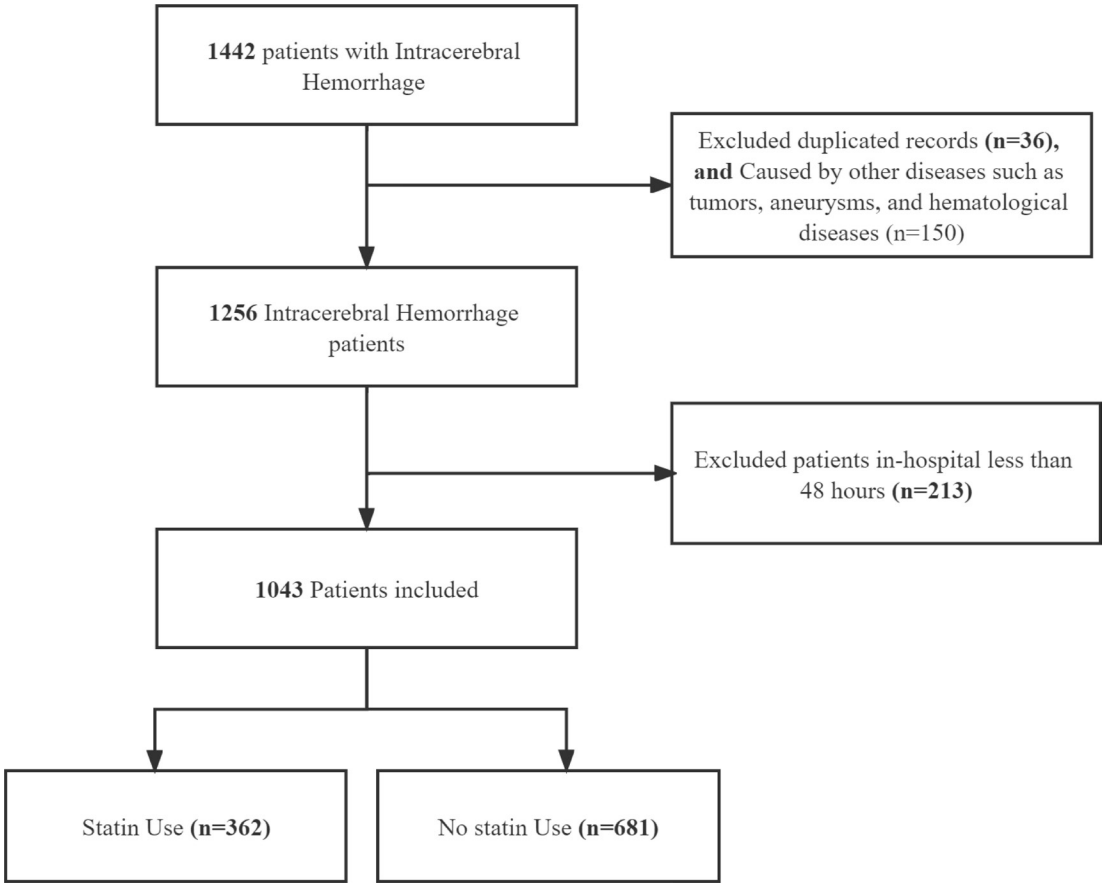

Figure 1 The flow chart of the study.

Table 1 Baseline characteristics of participants

Covariates	Total (n=1043)	No statin use (n=681)	Statin use (n=362)	P value
Age (years)	68.2±15.1	66.6±15.9	71.3±12.8	<0.001
Female, sex, n (%)	473 (45.3)	305 (44.8)	168 (46.4)	0.616
Ethnicity, n (%)				0.011
White	745 (71.4)	468 (68.7)	277 (76.5)	
Black	80 (7.7)	52 (7.6)	28 (7.7)	
Others	218 (20.9)	161 (23.6)	57 (15.7)	
Weight (kg)	76.9±18.4	75.7±18.1	79.1±18.9	0.005
Alcohol drinker, n (%)	85 (8.1)	65 (9.5)	20 (5.5)	0.024
Smoker, n (%)	119 (11.4)	67 (9.8)	52 (14.4)	0.029
Comorbidities, n (%)				
Atrial fibrillation	266 (25.5)	145 (21.3)	121 (33.4)	<0.001
Diabetes	241 (23.1)	111 (16.3)	130 (35.9)	<0.001
Hypertension	806 (77.3)	494 (72.5)	312 (86.2)	<0.001
COPD	93 (8.9)	54 (7.9)	39 (10.8)	0.125
Coronary	180 (17.3)	71 (10.4)	109 (30.1)	<0.001
Heart failure	146 (14.0)	81 (11.9)	65 (18)	0.007
Hyperlipidaemia	307 (29.4)	99 (14.5)	208 (57.5)	<0.001
Kidney	178 (17.1)	92 (13.5)	86 (23.8)	<0.001
Laboratory blood results				
White blood cell (10^9/L)	10.7±4.1	10.9±4.3	10.4±3.9	0.036
Blood platelet (10^9/L)	251.5±107.9	251.6±112.6	251.4±98.6	0.969
Blood neutrophil (%)	78.8±10.9	79.0±11.0	78.5±10.7	0.446
Blood lymphocyte (%)	13.2 (8.4, 16.9)	12.9 (8.2, 16.9)	13.7 (8.6, 17.0)	0.145
Blood monocyte (%)	4.3 (3.0, 5.3)	4.2 (3.0, 5.2)	4.5 (3.3, 5.5)	0.005
APTT(s)	29.0±9.8	28.4±8.7	30.1±11.6	0.008
PT(s)	14.0±3.3	14.0±3.1	14.1±3.6	0.542
Serum calcium (mg/dL)	8.7±0.7	8.7±0.7	8.7±0.6	0.933
Serum sodium (mg/dL)	139.5±4.7	139.7±4.8	139.2±4.5	0.084
Serum chlorine (mg/dL)	104.7±5.6	104.8±5.9	104.5±5.0	0.321
Serum potassium (mEq/L)	3.9±0.5	3.9±0.5	4.0±0.5	0.023
Blood glucose (mg/dL)	133.4±41.0	132.4±39.7	135.2±43.4	0.291
Serum creatinine (mg/dL)	0.8 (0.7, 1.1)	0.8 (0.6, 1.1)	0.9 (0.7, 1.2)	<0.001
Serum urea nitrogen (mg/dL)	19.0 (13.0, 26.0)	18.0 (13.0, 25.0)	20.0 (14.0, 28.0)	0.006
GCS score	11.5±3.7	11.2±3.8	12.1±3.4	<0.001
SOFA score	3.0 (2.0, 4.0)	3.0 (1.0, 4.0)	3.0 (2.0, 4.0)	0.632
Location of ICH, n (%)				0.774
Cerebral hemisphere	873 (83.7)	575 (84.4)	298 (82.3)	
Cerebellum	86 (8.2)	54 (7.9)	32 (8.8)	
Brainstem	40 (3.8)	26 (3.8)	14 (3.9)	
Ventricle	44 (4.2)	26 (3.8)	18 (5)	
Statin type, n (%)				<0.001
Atorvastatin	176 (16.9)	0 (0)	176 (48.6)	
Lovastatin	3 (0.3)	0 (0)	3 (0.8)	
Pravastatin	18 (1.7)	0 (0)	18 (5)	
Rosuvastatin	7 (0.7)	0 (0)	7 (1.9)	
Simvastatin	158 (15.1)	0 (0)	158 (43.6)	
90-day mortality, n (%)	311 (29.8)	227 (33.3)	84 (23.2)	<0.001

APTT, activated partial thromboplastin time; COPD, chronic obstructive pulmonary disease; GCS, Glasgow Coma Scale; ICH, intracerebral haemorrhage; PT, prothrombin time; SOFA, Sequential Organ Failure Assessment.

verified and evaluated using a multivariable Cox regression model. A one-to-one nearest neighbour matching algorithm was applied using a calliper width of 0.2. The following variables were selected to generate the propensity score: sex, age, atrial fibrillation, diabetes, coronary, heart failure, hyperlipidaemia, kidney, ethnicity, GCS score, SOFA score, location of ICH, white blood cell, blood platelet, serum sodium, serum chlorine, blood glucose, serum creatinine, serum urea nitrogen, APTT and PT. It was indispensable to calculate the HR for 90-day mortality, and then we used a univariable Cox proportional hazards regression model with the robust variance estimator; we also used the estimated propensity scores as weights and used an inverse probability weighting (IPW) model to generate a weighted cohort.[21] Univariable Cox proportional hazards regression was then performed to adjust the propensity score. Finally, 236 matched pairs were generated and applied to further analyses.

Statistical analysis

We conducted descriptive research on the data of all participants. For a normal distribution, continuous variables are expressed as mean±SD; for skewed distribution, continuous variables are expressed as median and quartile ranges. The Student's t-test, Wilcoxon rank-sum test or Kruskal-Wallis test were used as appropriate. Categorical variables are presented as numbers and percentages, and the χ^2 test was used. We used multivariable Cox regression analyses to assess the independent association between statin use and 90-day mortality. An extended Cox model approach was adopted for different covariates-adjusted models. We constructed three models: model 1, adjusted only for age and gender. Model 2 was additionally adjusted for atrial fibrillation, diabetes, coronary, heart failure, hyperlipidaemia and kidney. Model 3 was additionally adjusted for ethnicity, GCS score, SOFA score and location of ICH. Model 4 was additionally adjusted for white blood cells, blood platelet, serum sodium, serum chlorine, blood glucose, serum creatinine, serum urea nitrogen, APTT and PT. To assess confounding, covariates were entered into a Cox regression model in the basic model or eliminated the covariates in the complete model, and compared the regression coefficients. We mainly include covariates based on clinical experience and covariates that change the initial regression coefficient of more than

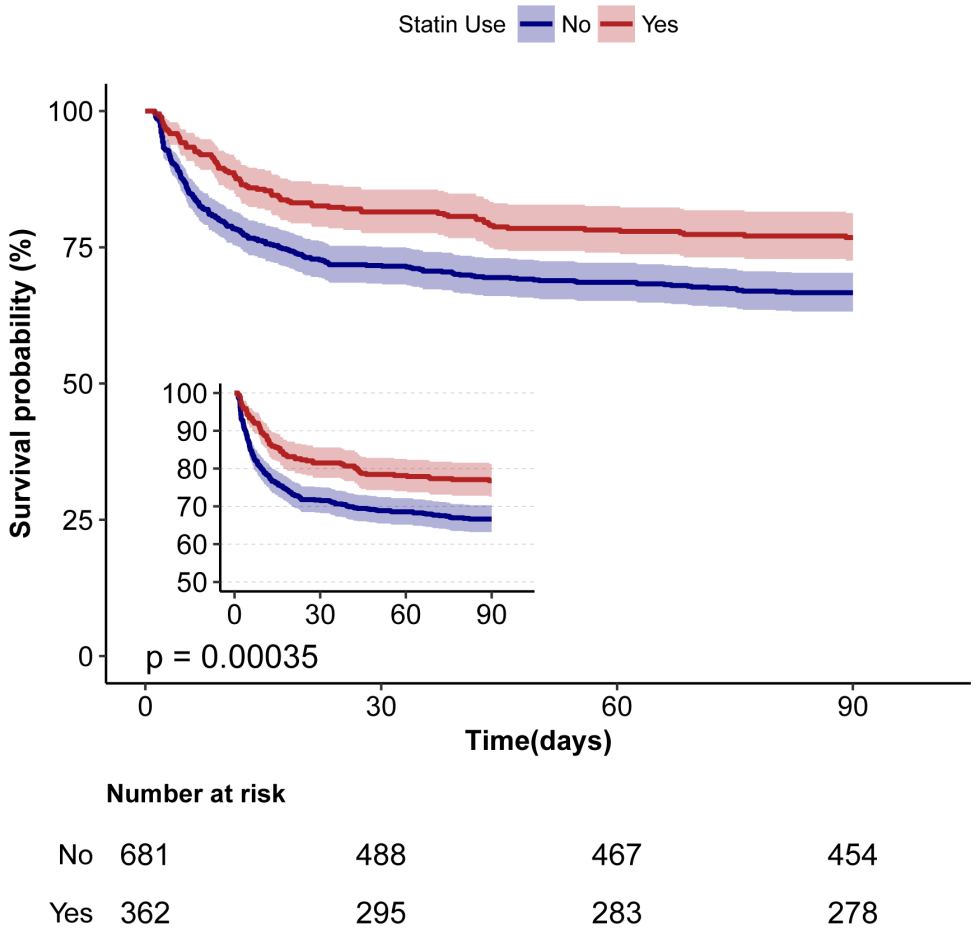

Figure 2 Kaplan-Meier survival curves for day 90 of intracerebral haemorrhage.

10%. In addition, survival curves were plotted by Kaplan-Meier (KM) and log-rank analyses.

Subgroup analyses were stratified by some relevant effect covariates. Including the following variables: age (<65 years vs ≥65 years), sex (female vs male), atrial fibrillation (no vs yes), heart failure (no vs yes) and hyperlipidaemia (no vs yes), heterogeneity among subgroups was assessed by multivariate Cox regression and interaction testing between subgroups. We also did a sensitivity analysis in addition to PSM to explain the relationship between statin use during hospitalisation and hospital mortality, 30-day mortality and 90-day mortality.

All analyses were performed using R V.3.6.3 (http://www.R-project.org, The R Foundation) and Free Statistics software V.1.71. P<0.05 (two-sided) was considered statistically significant.

Patient and public involvement

Patients and the public were not involved in the design, conduct or reporting of this study.

RESULTS

Patient characteristics and outcome

Of the total 1442 patients with ICH, 1043 patients were included. We excluded duplicated records and patients caused by other diseases, such as tumours, aneurysms and haematological diseases. In addition, we also excluded patients the in-hospital length was less than 48 hours. Finally, 1043 patients were enrolled in our study. Of these patients, 362 (34.7%) were statin users. The flow chart of the study is presented in figure 1. The baseline characteristics of all participants are listed in table 1. The age of all participants was 68.2±15.1; 473 (45.3%) were female, 745 (71.4%) were white individuals and 80 (7.7%) were black individuals. Patients who use statins were more likely to have complications in the past, such as atrial fibrillation, diabetes, hypertension, COPD, coronary, hyperlipidaemia, kidney stones and heart failure. The difference in blood platelet was slight between the groups (251.4±98.6 vs 251.6±112.6, p=0.969), and the SOFA score on admission was also relatively similar in the statin use and no statin use groups (3.0 (2.0, 4.0) vs 3.0 (1.0, 4.0), p=0.632). The site of cerebral haemorrhage was distributed in the cerebral hemisphere, cerebellum, brain stem and ventricle, which mainly occurs in the cerebral hemisphere, accounting for 83.7%. Atorvastatin was the most commonly used statin. The overall 90-day mortality was 29.8% (311/1043). The 90-day mortality for non-statin and statin users was 33.3% (227/681) and 23.2% (84/362), respectively.

Relationship between statin use and 90-day mortality

The KM curve showed lower mortality by day 90 in patients with statin use (log-rank test: p=0.00035, figure 2). In the

Table 2 Association between statin use and 90-day mortality using an extended model approach and propensity-score analyses

Analysis	HR of statin use	95% CI	P value
Crude model	0.64	(0.50 to 0.82)	<0.001
Model 1	0.56	(0.43 to 0.72)	<0.001
Model 2	0.52	(0.39 to 0.69)	<0.001
Model 3	0.63	(0.47 to 0.85)	<0.01
Model 4	0.71	(0.52 to 0.97)	<0.05
IPW*	0.69	(0.54 to 0.88)	<0.01
Propensity score matched†	0.67	(0.47 to 0.96)	<0.05
Propensity score adjusted‡	0.73	(0.54 to 0.97)	<0.05

Model 1: adjusted for sex and age.
Model 2: adjusted for the variables in model 1 plus atrial fibrillation, diabetes, coronary, heart failure, hyperlipidaemia and kidney.
Model 3: adjusted for the variables in model 2 plus ethnicity, Glasgow Coma Scale score, Sequential Organ Failure Assessment score and location of intracerebral haemorrhage.
Model 4: adjusted for the variables in model 3 plus white blood cell, blood platelet, serum sodium, serum chlorine, blood glucose, serum creatinine, serum urea nitrogen, activated partial thromboplastin time, prothrombin time.
*Primary analysis with an HR from the multivariable Cox proportional-hazards model with the same strata and covariates as model 4 with inverse probability weighting according to the propensity score.
†HR from a multivariable Cox proportional-hazards model with the same strata and covariates as model 4 with matching according to the propensity score.
‡HR from a multivariable Cox proportional-hazards model with the same strata and covariates as model 4, with additional adjustment for the propensity score.
IPW, inverse probability weighting.

extended multivariable Cox models (table 2), we observed that the HRs of statin use were consistently significant in crude model and all four adjusted models (HRs range 0.52–0.71, p<0.05 for all). After adjustment for all covariates in table 1, a 29% lower of 90-day mortality could be shown in patients with statin use (HR=0.71, 95% CI 0.52 to 0.97, p<0.05, model 4, table 2). IPW also demonstrated a significantly lower 90-day mortality in statin users. The HR was 0.69 (95% CI 0.54 to 0.88, p<0.01) (table 2).

Subgroup analysis was performed according to the confounders, including age, sex, atrial fibrillation, heart failure and hyperlipidaemia; we found that statin use during hospitalisation was associated with lower ICH mortality, which was more common in patients with hyperlipidaemia. The HR was 0.38 (95% CI 0.23 to 0.66, p<0.001). We did not observe any significant interaction in the subgroups (figure 3). Although the p values for interactions for hyperlipidaemia were lower than 0.05, the result may not have significant clinical implications given multiple testing and similar directionality of the associations.

Outcomes after PSM

After PSM, 236 pairs of each group were well-matched by a 1:1 matching algorithm (table 3 and online supplemental material). The overall quality of the matched sample was assessed by comparing the standardised difference of the means and the ratio of the variances between the propensity scores of both groups and graphically inspecting the

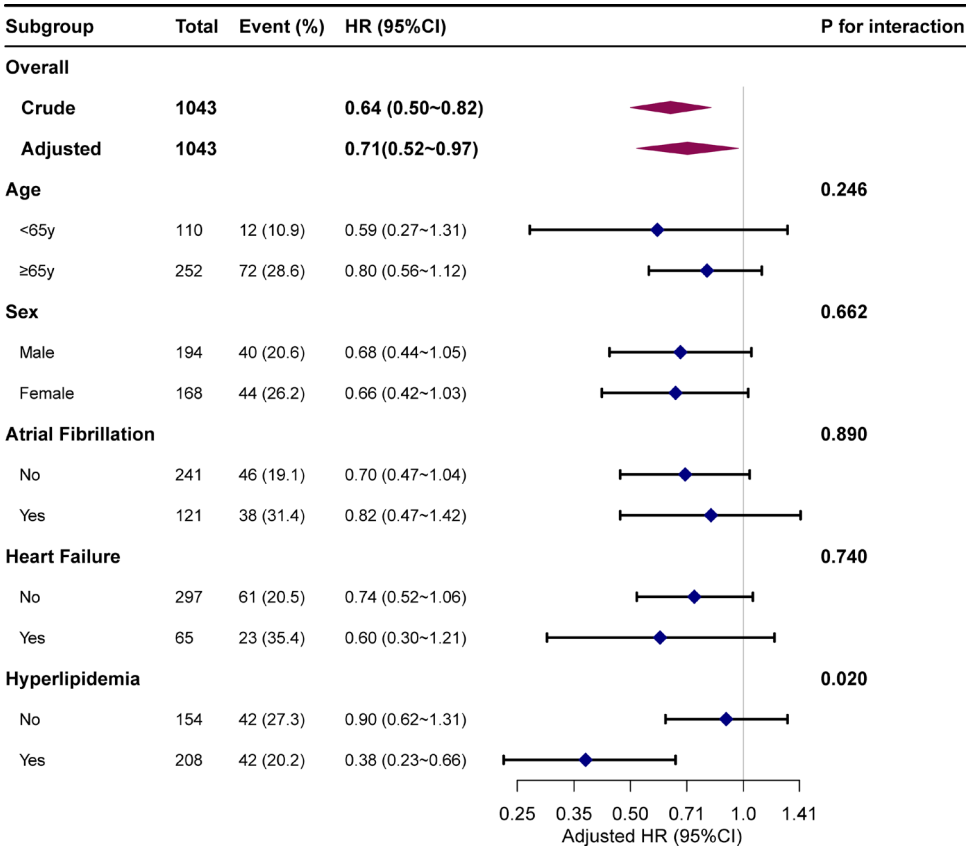

Figure 3 Stratified analyses by potential modifiers of the association between statin use and the risk of 90-day mortality.

Table 3 Comparisons of the covariates after propensity score matching

Covariates	Total (n=472)	No statin use (n=236)	Statin use (n=236)	P value
Age (years)	70.7±13.0	70.7±13.4	70.8±12.6	0.977
Female, sex, n (%)	240 (50.8)	113 (47.9)	127 (53.8)	0.197
Ethnicity, n (%)				0.312
White	339 (71.8)	166 (70.3)	173 (73.3)	
Black	35 (7.4)	15 (6.4)	20 (8.5)	
Others	98 (20.8)	55 (23.3)	43 (18.2)	
Weight (kg)	76.5±18.4	75.4±17.4	77.6±19.2	0.192
Alcohol drinker, n (%)	26 (5.5)	12 (5.1)	14 (5.9)	0.687
Smoker, n (%)	55 (11.7)	25 (10.6)	30 (12.7)	0.473
Comorbidities, n (%)				
Atrial fibrillation	136 (28.8)	71 (30.1)	65 (27.5)	0.542
Diabetes	132 (28.0)	64 (27.1)	68 (28.8)	0.682
Hypertension	381 (80.7)	187 (79.2)	194 (82.2)	0.414
COPD	41 (8.7)	21 (8.9)	20 (8.5)	0.87
Coronary	103 (21.8)	58 (24.6)	45 (19.1)	0.147
Heart failure	70 (14.8)	41 (17.4)	29 (12.3)	0.12
Hyperlipidaemia	189 (40.0)	90 (38.1)	99 (41.9)	0.398
Kidney	76 (16.1)	46 (19.5)	30 (12.7)	0.045
Laboratory blood results				
White blood cell (10^9/L)	10.6±3.9	10.7±4.1	10.6±3.8	0.815
Blood platelet (10^9/L)	257.9±107.4	254.2±113.4	261.7±101.1	0.451
Blood neutrophil (%)	78.9±10.0	79.0±10.1	78.8±9.9	0.877
Blood lymphocyte (%)	13.3 (8.3, 16.8)	13.1 (7.8, 17.0)	13.4 (8.6, 16.7)	0.411
Blood monocyte (%)	4.3 (3.0, 5.3)	4.2 (3.0, 5.3)	4.4 (3.0, 5.3)	0.467
APTT(s)	29.2±10.0	29.4±10.0	29.1±10.0	0.704
PT(s)	13.9±3.3	14.0±3.4	13.8±3.2	0.605
Serum calcium (mg/dL)	8.8±0.7	8.8±0.7	8.8±0.6	0.813
Serum sodium (mg/dL)	139.1±4.5	139.1±4.3	139.2±4.7	0.910
Serum chlorine (mg/dL)	104.4±5.5	104.4±5.8	104.4±5.1	1.000
Serum potassium (mEq/L)	3.9±0.5	3.9±0.5	3.9±0.5	0.462
Blood glucose (mg/dL)	132.7±42.1	132.3±41.9	133.2±42.3	0.810
Serum creatinine (mg/dL)	0.8 (0.6, 1.1)	0.8 (0.7, 1.2)	0.8 (0.6, 1.0)	0.019
Serum urea nitrogen (mg/dL)	19.0 (13.0, 26.0)	19.0 (14.0, 27.0)	19.0 (13.0, 25.0)	0.085
GCS score	11.8±3.5	11.9±3.5	11.7±3.4	0.577
SOFA score	3.0 (2.0, 4.0)	3.0 (1.8, 4.0)	3.0 (2.0, 4.0)	0.756
Location of ICH, n (%)				0.869
Cerebral hemisphere	393 (83.3)	194 (82.2)	199 (84.3)	
Cerebellum	40 (8.5)	22 (9.3)	18 (7.6)	
Brainstem	19 (4.0)	9 (3.8)	10 (4.2)	
Brainstem	20 (4.2)	11 (4.7)	9 (3.8)	
Statin type, n (%)				<0.001
Atorvastatin	109 (23.1)	0 (0)	109 (46.2)	
Lovastatin	1 (0.2)	0 (0)	1 (0.4)	
Pravastatin	9 (1.9)	0 (0)	9 (3.8)	
Rosuvastatin	5 (1.1)	0 (0)	5 (2.1)	
Simvastatin	112 (23.7)	0 (0)	112 (47.5)	
90-day mortality, n (%)	127 (26.9)	74 (31.4)	53 (22.5)	0.029

APTT, activated partial thromboplastin time; COPD, chronic obstructive pulmonary disease; GCS, Glasgow Coma Scale; ICH, intracerebral haemorrhage; PT, prothrombin time; SOFA, Sequential Organ Failure Assessment.

propensity scores between the groups. There was no significant difference between the two matched groups. Among the 236 propensity-matched pairs, we found that the 90-day mortality was significantly lower in the statin user group (53 (22.5%) vs 74 (31.4%), p<0.05). In univariable Cox proportional hazards regression, the HR was 0.67 (95% CI 0.47 to 0.96, p<0.05). Additional adjustment for the propensity score also demonstrated a significantly lower 90-day mortality in statin users. The HR was 0.73 (95% CI 0.54 to 0.97, p<0.05).

Sensitive analysis

We further discussed the short-term and long-term effects of statin use on patients with ICH. After adjusting all the covariates after screening, multivariate regression model analysis showed that statin use during hospitalisation was related to the reduction of in-hospital mortality (HR=0.67, 95% CI 0.46 to 0.97, p<0.05), 30-day mortality (HR=0.70, 95% CI 0.50 to 0.99, p<0.05) and 1-year mortality (HR=0.75, 95% CI 0.57 to 0.98, p<0.05). The results remain stable in IPW and PSM analyses. Our results were also intuitively shown by KM curve analysis (online supplemental material).

DISCUSSION

In this relatively large-scale cohort study, we found that statin users had a lower risk-adjusted 90-day mortality than patients who did not use it. This result remained robust in the comparisons after PSM and IPW.

Data from a previous study demonstrated an association between statin use before ICH and reduced mortality (OR=0.47, 95% CI 0.32 to 0.70) at 90 days, and they also conducted a meta-analysis of all published evidence confirmed the effect of statin use on lower mortality (OR=0.55, 95% CI 0.42 to 0.72) after ICH.[12] Their results are akin to our findings. However, in this paper, OR was used to evaluate the mortality with 90-day follow-up, which we thought should be analysed by HR using Cox

regression analysis, which may have different results. They overlooked several important confounders, such as SOFA score and platelet count. Our study used a comprehensive model approach to adjust the potential confounders and found a stable relationship between statin use and 90-day mortality.

Eichel *et al* conducted a retrospective cohort study on 399 patients. They concluded that statin treatment did not significantly impact mortality or functional outcome on multiple logistic regression analysis.[22] Compared with our study, their sample size is smaller, and many admission laboratory indicators, GCS scores and SOFA scores are poorly controlled. Furthermore, results from another study also suggested no link between statin use and outcome after ICH.[15] In the Lin' cohort,[11] patients who received statin therapy were associated with lower risks of all-cause mortality (12.7% vs 21.3%; HR 0.54; 95% CI 0.45 to 0.65) only for dyslipidaemia patients, which is similar to our research. A multicentre prospective study conducted by Siddiqui and colleagues[23] showed that there was a significantly higher risk of death (in-hospital or postdischarge within 3 months) and disability (3-month Modified Rankin Scale) among non-statin users, compared with statin users, suggesting that continued or new use of statins after hospitalisation may thus be associated with better outcome in statin users. This is consistent with our findings, but the authors did not adjust the statin type information, the long-term effect of statin on ICH is also not mentioned, and the propensity score was based on a small number of statin users. In our study, we further adjusted the information of multiple variables, such as the type of statins, through covariate screening and carried out multi-model regression analysis, PSM and inverse probability weighted analysis, all of which confirmed that our results were very stable. At the same time, through sensitivity analysis, we found that using statins during hospitalisation may be beneficial to the in-hospital mortality, 30-day mortality and 1-year mortality of patients with ICH, which needs to be confirmed by extensive sample prospective studies in the future.

The mechanism of statin use and ICH mortality reduction is still unclear. We consider that statins can not only reduce blood lipids and stabilise atherosclerotic plaques, thus reducing the incidence and mortality of cardiocerebrovascular diseases, but also bring other 'multiple effects',[24] such as inhibiting inflammation, reducing oxidative stress and improving endothelial function. This may also explain why statin use during hospitalisation was associated with lower ICH mortality, which was more common in patients with hyperlipidaemia. The HR was 0.38 (95% CI 0.23 to 0.66, p<0.001). Studies have shown that in animal experiments, statins may prove the ability to increase ICH mortality by promoting neuronal plasticity and limiting boundary tissue damage, increasing cerebral blood flow and anti-inflammatory properties, and improving angiogenesis and nerve regeneration after ischaemic injury.[25] There is also evidence that statins have beneficial effects on ICH related to neuroprotective activities or reduced haematoma volume.[26] The withdrawal of statins may lead to rebound effects, leading to oxidative stress and vascular dysfunction.[27] These findings may also help explain the beneficial effects of statins on ICH. In addition, in some basic studies, statins have been found to inhibit the occurrence of epilepsy and have anticonvulsant effects in epileptic animal models.[28 29] In addition, the use of statins can reduce the risk of clinical epilepsy.[30 31] Several studies have shown that the use of statins is associated with reducing the risk of epilepsy after stroke.[32 33] Patients with ICH have a high mortality rate caused by epilepsy, which may also explain why statins can reduce mortality at this level.

There are some limitations to our study. First of all, as with all retrospective analyses, there may be potential residual confounding factors in our study, although we adjusted all possible confounding factors as much as possible and minimised the impact of factors that could lead to biased results through PSM and IPW. Second, since the study population only includes patients with ICH, it may not be extended to patients with subarachnoid haemorrhage caused by brain trauma or aneurysms. Third, we could not identify the specific aetiology of ICH, which led to the failure to conduct a more detailed subgroup analysis of the causes. Fourth, we could not obtain data on the dose of statins in this study, and there was no dose–response analysis. We are unable to obtain the volume of ICH and previously used antithrombotic drugs, which may have some impact on the results. Fifth, in the 'admission medication', the use of statins may be more likely not to be recorded in this study. There are fewer statins with ICH in our study than previously reported. However, it is worth noting that the misclassification of potential exposure caused by this error tends to be null, resulting in an underestimation of the association between statin use and 90-day mortality. Finally, the cause of death is not recorded in the MIMIC-III database, and we cannot conduct a competitive risk analysis.

CONCLUSION

Our findings suggested that statin use was associated with lower risk-adjusted mortality in patients with ICH. This association warrants further investigation.

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