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Retraction

Retracted: Statins on Spontaneous Intracerebral Hemorrhage: A Meta-Analysis

Evidence-Based Complementary and Alternative Medicine

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This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope

(2) Discrepancies in the description of the research reported

(3) Discrepancies between the availability of data and the research described

(4) Inappropriate citations

(5) Incoherent, meaningless and/or irrelevant content included in the article

(6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

References

[1] X. Liu, W. Luo, H. Huang, and J. Fan, "Statins on Spontaneous Intracerebral Hemorrhage: A Meta-Analysis," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 2342159, 11 pages, 2022.

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Research Article

Statins on Spontaneous Intracerebral Hemorrhage: A Meta-Analysis

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Objective. In order to explore whether the application of statins can improve the prognosis of patients with intracerebral hemorrhage. *Methods*. Studies of patients with intracerebral hemorrhage taking statins published in English until December 2021 were searched based on limited search terms, the retrieved literature was screened out based on inclusion and exclusion criteria, and the quality assessment and data extraction were carried out independently by two investigators. The extracted clinical data were then meta-analyzed. *Results*. A total of 17 literatures were included in this study, with a sample size of 16,988 cases, including 3,001 cases in the statin group and 13,487 cases in the control group. MRS score of mortality was used as the prognostic index to evaluate cerebral hemorrhage. According to the Newcastle-Ottawa Scale (NOS), the score of literature quality evaluation scale was 6–8, indicating good literature quality. Meta-analysis of clinical data extracted from the literature showed that the statin group reduced overall mortality after intracerebral hemorrhage compared with the nonstatin group ($P < 0.01$). In terms of improving functional prognosis, the statin group improved functional prognosis 90 days after intracerebral hemorrhage ($P = 0.01$). There was no significant difference between the statin and nonstatin groups in reducing the number of intracerebral hematomas. *Conclusions*. Statins can reduce the total mortality after ICH and improve the survival rate (90 d), without increasing the amount of hematoma.

1. Background

Spontaneous intracerebral hemorrhage (ICH) [1], as a primary nontraumatic parenchymal hemorrhage, is a subtype with the worst prognosis of stroke, the one-month mortality approaching 40% and 75%. Patients with ICH often cannot take care of themselves, mild patients were with disabilities and other sequelae and loss of work ability, and severe patients can die from intracerebral hemorrhage acute phase or long-term complications [2]. Despite the rapid progress in the medical field in recent years, many cerebrovascular diseases can be effectively treated, such as drug therapy and intravascular interventional therapy, but ICH still has a high mortality and disability rate, its prognosis is not optimistic, and there is still a lack of effective treatment [3].

Statins [4], hydroxymethyl glutaryl-CoA (HMG-CoA) reductase inhibitors, originated from fungi and had a history of more than 40 years ago. On the one hand, statins competitively inhibit key steps in the cholesterol biosynthesis pathway by binding to enzyme substrates, limiting cholesterol synthesis, and reducing cholesterol concentration in the liver [5]. On the other hand, statins also increase the clearance rate of LDL-cholesterol particles in the blood by upregulating LDL receptor expression on the liver membrane [6]. Because statins can lower blood lipids well, they play an important role in ischemic heart and cerebrovascular diseases based on antiatherosclerosis, which is also inseparable from the wide range of applications of statins [7]. Therefore, statins are widely used in the primary and secondary prevention of cardiovascular and cerebrovascular diseases [8]. In recent years, some animal

experiments and basic studies have shown that statins can improve the prognosis of cerebral hemorrhage. They have anti-inflammatory activities, maintain vascular endothelial stability, upregulate nitric oxide synthase, and stimulate neurogenesis and synaptic formation, thus achieving neuroprotective effects [9]. An experimental study on stroke in 2004 [10] suggested that statins can be used in a variety of complex situations such as hemorrhage transformation after acute ischemic stroke, hemorrhage after thrombolytic therapy, and acute phase of cerebral hemorrhage. However, a study in 2006 [11] suggested that statins promoted hematoma enlargement, increased the risk of rebleeding, and increased ICH mortality or functional outcomes by inhibiting platelet aggregation and thrombosis. SPARCL test [12] and SPARCL secondary analysis [13] both showed that statins increased the risk of cerebral hemorrhage [14].

There is still a lack of evidence-based medical evidence on whether statins reduce the incidence and improve the prognosis of intracerebral hemorrhage. This paper conducted a meta-analysis of 17 included literature, in order to provide evidence for clinical treatment of intracerebral hemorrhage.

2. Materials and Methods

2.1. Search Strategy. A comprehensive search of PubMed, Medline, Embase, Web of Science, and The Cochrane Library was limited to high-quality studies published until December 2021. The included literature was searched to find the studies that met the inclusion criteria. Search terms included intracerebral hemorrhage, ICH, intracranial bleeding, statins, and prognosis of cerebral hemorrhage.

2.2. Inclusion and Exclusion Criteria. Inclusion criteria are as follows: (1) study type: study comparing the prognosis of intracranial hemorrhage between the statin group and the nonstatin group; (2) there were no statistically significant differences in gender, mean age, past medical history, and other basic characteristics between the statin group and the nonstatin group; (3) the diagnostic criteria were spontaneous intracerebral hemorrhage confirmed by head CT; (4) outcome indicators: mortality (in-hospital, 30 d, 90 d, long-term), functional score (MRS 0–3/MRS 0–2) in different periods after intracerebral hemorrhage (in-hospital, 30 d, 90 d, long-term) and hematoma; (5) original research report; (6) rigorous experimental design and reliable data.

Exclusion criteria are as follows: (1) head CT clearly does not meet the diagnostic criteria of cerebral hemorrhage; (2) the prognosis of intracerebral hemorrhage was affected by other drugs (antiplatelet drugs, anticoagulants, etc.); patients with subarachnoid and subdural hemorrhage, hemorrhagic transformation of ischemic stroke, hemorrhage due to brain tumors and arteriovenous malformations; (3) secondary cerebral hemorrhage, such as brain trauma; (4) case report and review; (5) literatures with repeated reports and poor data quality; (6) the sample size is too small ($n < 10$), and the original data are incomplete and cannot be obtained through other means.

2.3. Quality Evaluation. The New Castle-Ottawa Scale (NOS) was used to evaluate the literature quality of the included literature, and a score of 6–8 indicated good literature quality [15].

2.4. Data Extraction. After the data extraction criteria were established, two trained evaluators comprehensively searched all databases according to keywords, independently selected the studies that met the inclusion criteria and extracted sample data. The missing data were obtained from the authors as far as possible, and the literature that could not obtain complete data information were abandoned. Finally, the basic features of the selected literature were, respectively, made into data extraction tables, in which part of the data need to be calculated, replaced, and merged, and finally verified the extracted data. In case of any disagreement in the process of data extraction, two people should negotiate to solve it. If there is still any disagreement, the third party (experienced evaluator) should be sought for assistance to solve it.

2.5. Statistical Analysis. Rate ratios (RRs) and 95% confidence intervals (CIs) were a result of categorical variables comparison and standardized mean difference (SMD) was a result of the continuous variable comparison to assess heterogeneity between studies using standard I^2 tests. The random effects model (RM) was selected for $I^2 > 50\%$, and the fixed effects model (FM) was selected for $I^2 < 50\%$. After the forest plot and funnel plot were made, studies with high heterogeneity were removed and analyzed again. All calculations were performed using statistical software provided by the Cochrane Collaboration (RevMan 5.3).

3. Results

3.1. Basic Information of the Included Studies. Seventeen studies [12, 16–31] finally met relevant standards, and the screening process is shown in Figure 1. The basic information of the included literature is shown in Table 1.

3.2. Effects of Statins on Mortality after ICH

3.2.1. Effects of Statins on Total Mortality after ICH. Sixteen studies [12,16–22,24–31] were included, including 3501 cases in the statin group and 13487 cases in the nonstatin group. The mortality rates during the last recorded period were statistically analyzed, and a meta-analysis was conducted, indicating heterogeneity $P < 0.001$, $I^2 = 84\% > 50\%$. The RM was used for the statistics, and the results were $P = 0.07$, RR = 0.86, 95% CI (0.73, 1.01), with no statistical significance. Results are shown in Figure 2.

3.2.2. Publish Bias Analysis. The funnel plot of literature was drawn by RevMan 5.3 to evaluate the publication bias of the included literature, as shown in Figure 3. Studies by Priglinger et al. and Pan et al. were obviously outside the confidence interval and increased heterogeneity.

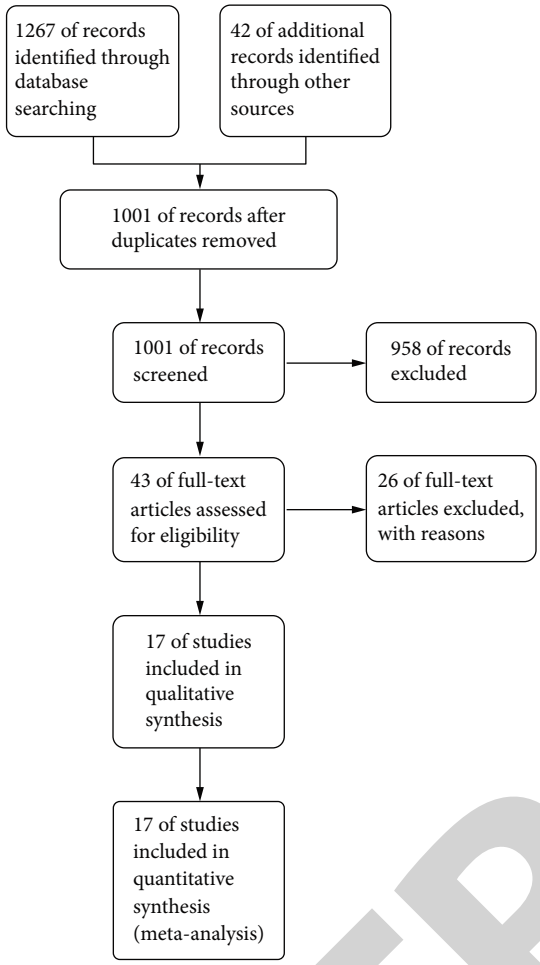

Figure 1: Flow diagram of the study selection process.

After excluding the studies conducted by Priglinger et al. [27] and Pan et al. [26], the forest plot of the other 10 literatures included showed $I^2 = 49\% < 50\%$. The fixed effect model was adopted, $P = 0.0005 < 0.05$, RR = 0.85, 95% CI (0.78, 0.93), indicating that statins are significant in reducing mortality after intracerebral hemorrhage (Figure 4).

After eliminating the studies conducted by Priglinger et al. [27] and Pan et al. [26], the funnel plot was symmetrically distributed with low heterogeneity (Figure 5).

3.2.3. Effects of Statins on In-Hospital Mortality after ICH. Six studies [17, 22, 24, 28, 30, 31] including in-hospital mortality were included, and heterogeneity showed $P < 0.01$, $I^2 = 89\% > 50\%$. The random effect model was used to conduct statistics, and the results were $P = 0.14$, RR = 0.79, 95% CI (0.57, 1.08), with no statistical significance (Figure 6).

3.2.4. Effects of Statins on 30 d, 90 d, and Long-Term Mortality after ICH. Three studies [17, 21, 25] were included, heterogeneity analysis showed $P = 0.23$, $I^2 = 31\% < 50\%$, fixed effect model was used for analysis. The difference, $P = 0.77$, RR = 1.02, 95% CI (0.88, 1.19), was not statistically significant. There was no significant difference in 30-day mortality after reduced intracerebral hemorrhage between the statin and nonstatin groups.

Ten studies were included [6, 16, 18–20, 24, 26, 27, 29, 30]. Heterogeneity analysis showed $P < 0.01$, $I^2 = 86\% > 50\%$. The random effect model was used to conduct the analysis, and the results were $P = 0.15$, RR = 0.84, 95% CI (0.67, 1.07), with no statistically significant difference. There was no significant difference between statins and non-statins in reducing 90 days post-ICH mortality.

Four studies [17, 24, 26, 31] were included, including 1 study [17] with half-year mortality and 3 studies [24, 26, 31] with 1-year mortality. Heterogeneity analysis showed $P < 0.01$, $I^2 = 92\% > 50\%$. The random effect model was used for analysis, and the results were $P = 0.09$, RR = 0.73, 95% CI (0.50, 1.06), the difference was not statistically significant, indicating that there was no significant difference between statins and non-statins in reducing long-term mortality after ICH (Figure 7).

The source of heterogeneity was analyzed, sensitivity analysis was conducted by funnel plot, and the heterogeneity of Mustanoja et al. [24], Pan et al. [26], Priglinger et al. [27], and Siddiqui et al. [30] with high heterogeneity was eliminated, which significantly reduced the heterogeneity. Results: $I^2 = 13\%$, using the fixed effect model, $P = 0.01 < 0.05$, RR = 0.87, 95% CI (0.78, 0.97), the difference is significant, indicating that statins can reduce the mortality of 90 days after ICH (Figure 8).

3.3. Effects of Statins on Functional Recovery after ICH

3.3.1. Effects of Statins on Total Functional Recovery after ICH. Eleven studies [6, 16–18, 20, 22, 24–27, 30] including functional prognosis after ICH were included, and a good functional prognosis was defined as MRS 0–3. The sample size of the statin group was 2779 cases, and that of the nonstatin group was 11387 cases. Meta-analysis showed that heterogeneity was $P < 0.01$, $I^2 = 90\% > 50\%$. The random effects model was used for analysis, and the results were $P = 0.20$, RR = 1.11, 95% CI (0.94, 1.32), with no statistical significance (Figure 9).

Sensitivity analysis was conducted, and heterogeneity was significantly reduced after the studies by Dowlatshali et al. [17], Pan et al. [26], and Priglinger et al. [27] were removed, $I^2 = 49\% < 50\%$, and the fixed effect model was adopted. The results showed that $P < 0.01$, RR = 1.12, 95% CI (1.05,1.20) had a significant difference. It indicates that statins can improve the functional prognosis of cerebral hemorrhage (Figure 10).

3.3.2. Effects of Statins on Functional Recovery during Hospitalization after ICH. Four studies [17, 22, 24, 25] including functional prognosis in hospitals after ICH were included. Heterogeneity showed $P < 0.01$, $I^2 = 79\% > 50\%$. The random effect model was used for analysis, and the results were $P = 0.57$, RR = 1.09, 95% CI (0.81, 1.46), with no statistically significant difference (Figure 11).

Table 1: Characteristics of included studies.

Author, year	Design	Research center	State	Group	Samples	Statin doses	Years	Outcomes	Follow-up	NOS
Biffi, 2011 [16]	Prospective	Single-center	USA	Statin	238	NA	74.2	Mortality, MRS	90 d	8
				Control	461		72			
Dowlatshah, 2012 [17]	Prospective	Multicenter	Canada	Statin	537	NA	74	Mortality, MRS	In the hospital, 30 d, 180 d	8
				Control	1929		70			
Eichel, 2010 [18]	Retrospective	Single-center	Israel	Statin	101	NA	72.4	Mortality, MRS	90 d	8
				Control	298		71.8			
FitzMaurice, 2008 [19]	Prospective	Single-center	USA	Statin	149	NA	72.4	Mortality, hematoma	90 d	8
				Control	480		71.9			
Goldstein, 2009 [6]	Retrospective	Single-center	England	Statin	44	80 mg	NA	Mortality, MRS	90 d	7
				Control	29		NA			
Gomis, 2010 [20]	Retrospective	Single-center	Spain	Statin	34	10–40 mg	73.6	Mortality, MRS	90 d	8
				Control	234		71.7			
King, 2012 [21]	Prospective	Single-center	Singapore	Statin	292	NA	66.7	Mortality, hematoma	30 d	8
				Control	1089		63.4			
Leker, 2009 [22]	Prospective	Multicenter	Israel	Statin	89	NA	70.9	Mortality, MRS	In the hospital	8
				Control	223		72.75			
Miura, 2011 [23]	Retrospective	Single-center	Japan	Statin	56	80 mg	73	MRS, hematoma	30 d	7
				Control	235		66.7			
Mustanoja, 2013 [24]	Retrospective	Single-center	Finland	Statin	187	NA	74	Mortality, MRS, hematoma	In the hospital, 30 d, 1y	8
				Control	777		65			
Naval, 2008 [25]	Retrospective	Single-center	USA	Statin	32	NA	69.8	Mortality, MRS, hematoma	In the hospital, 30 d	7
				Control	93		61.3			
Pan, 2014 [26]	Prospective	Multicenter	China	Statin	220	NA	60.7	Mortality, MRS	90 d, 1 y	8
				Control	2998		62.2			
Priglinger, 2015 [27]	Prospective	Multicenter	multiple countries	Statin	204	NA	NA	Mortality, MRS, hematoma	90 d	7
				Control	2980		NA			
Ricard, 2010 [28]	Retrospective	Multicenter	Canada	Statin	71	NA	71.1	Mortality, hematoma	In the hospital	8
				Control	232		74.9			
Romero, 2011 [29]	Prospective	Single-center	Brazil	Statin	20	2–8 mg/kg	68	Mortality, GCS	90 d	8
				Control	62		69			
Siddiqui, 2017 [30]	Prospective	Multicenter	USA	Statin	1093	NA	65.1	Mortality, MRS, hematoma	In the hospital, 90 d	9
				Control	1364		60.3			
Winkler, 2013 [31]	Retrospective	Single-center	USA	Statin	190	NA	70.4	Mortality, hematoma	In the hospital, 1 y	8
				Control	236		67			

Study or Subgroup	statin Events	statin Total	Control Events	Control Total	Weight (%)	Risk Ratio M-H, Random, 95% CI
Biffi 2011	109	238	267	461	8.1	0.79 [0.67, 0.93]
Dowlatshahi 2012	231	537	828	1929	8.4	1.00 [0.90, 1.12]
Eichel 2010	43	101	132	298	7.1	0.96 [0.74, 1.25]
FitzMaurice 2008	68	149	216	480	7.7	1.01 [0.83, 1.24]
Goldstein 2009	14	44	15	29	4.3	0.62 [0.35, 1.07]
Gomis 2010	9	34	77	235	4.0	0.81 [0.45, 1.46]
King 2012	92	292	302	1089	7.8	1.14 [0.94, 1.38]
Leker 2009	19	89	66	223	5.2	0.72 [0.46, 1.13]
Mustanoja 2013	69	187	268	777	7.6	1.07 [0.87, 1.32]
Naval 2008	5	32	24	93	2.4	0.61 [0.25, 1.45]
Pan 2014	19	220	819	2998	5.3	0.32 [0.20, 0.49]
Priglinger 2015	42	204	338	2980	6.8	1.82 [1.36, 2.42]
Ricard 2010	32	71	88	232	6.7	1.19 [0.88, 1.61]
Romero 2011	8	20	30	63	4.0	0.84 [0.46, 1.52]
Siddiqui 2017	191	1093	355	1364	8.1	0.67 [0.57, 0.79]
Winkler 2013	39	190	86	236	6.4	0.56 [0.41, 0.78]
Total (95% CI)		*3501*		*13487*	*100.0*	*0.86 [0.73, 1.01]*
Total events	*990*		*3911*			

Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 91.73$, $df = 15$ ($P < 0.00001$); $I^2 = 84\%$
Test for overall effect: $Z = 1.83$ ($P = 0.07$)

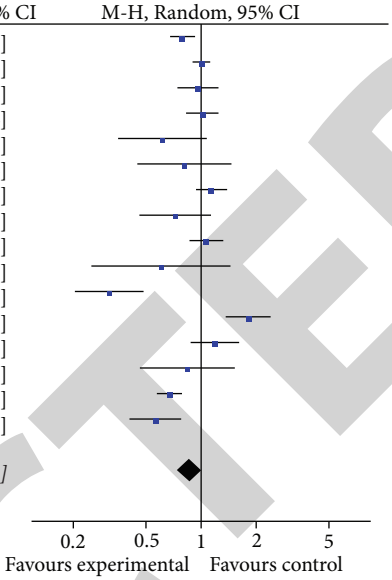

Figure 2: Meta-analyses of statin versus no-statin treatment in intracerebral hemorrhage for total mortality.

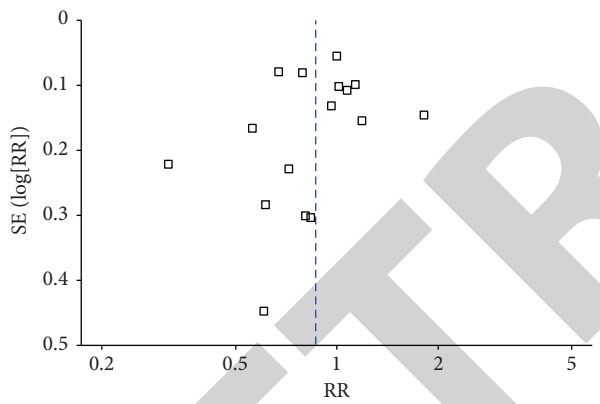

Figure 3: Funnel plot of the effect of statins on total mortality after intracerebral hemorrhage.

3.3.3. Effects of Statins on Functional Recovery 90 Days after ICH (MRS 0–3). Five studies [6, 18, 20, 26, 30] containing functional prognosis at 90 days after ICH were included, in which a good functional prognosis was defined as MRS 0–3, heterogeneity showed $P < 0.01$, $I^2 = 90\% > 50\%$. The random effect model was used for analysis, and the results were $P = 0.04$, RR = 1.25, 95% CI (1.01, 1.55), and the difference was statistically significant (Figure 12).

Sensitivity analysis was performed, excluding heterogeneous source studies (Pan et al. [26]), $I^2 = 19\%$, and the results were as follows: $P = 0.01$, RR = 1.10, 95% CI (1.02, 1.18), indicating that statins can improve the medium and long-term prognosis after ICH (Figure 13).

3.3.4. Effects of Statins on Functional Recovery 90 Days after ICH (MRS 0–2). Seven studies [6, 16, 18, 20, 26, 27, 30] containing functional outcomes at 90 days after ICH were included, in which a good functional prognosis was defined as MRS 0–2 points, heterogeneity was $P < 0.01$, $I^2 = 93\% > 50\%$, and random effects model was used to perform analysis, $P = 0.68$, RR = 1.06. 95% CI (0.80, 1.42), the difference was not statistically significant (Figure 14).

3.4. Effects of Statins on Hematoma Formation after ICH. Seven studies [16, 19, 21, 23, 24, 28, 30] containing the volume of hematoma after ICH were included, of which 4 studies used the mean value as a numerical variable, and the other 3 studies used the median value as a numerical variable. Four studies with average were analyzed, and the median of three literature was estimated as the average. Since the sample size was greater than 70, the mean $X \approx (a + 2m + b)/4$, SD = (Max–Min)/6 were adopted. After conversion, the above four studies were analyzed, and the results showed that $P = 0.01$, SMD = 0.48, 95% CI (0.10, 0.86), with high heterogeneity, the results were not credible and could not prove that statins increased the amount of cerebral hemorrhage (Figure 15).

4. Discussion

ICH is a fatal disease with no specific treatment to improve the prognosis. Primary ICH etiology can be divided into hypertension and cerebral amyloid vascular disease (CAA), secondary ICH risk factors are brain tumor, aneurysm, arteriovenous malformation, coagulation abnormalities, brain trauma, etc. [32]. HMG-CoA reductase inhibitors (statins) are common lipid-lowering drugs in clinical practice, which can effectively reduce LDL and cholesterol levels, and are widely used in the primary and secondary prevention of cardiovascular and cerebrovascular diseases based on atherosclerosis [33]. However, epidemiological studies have shown that hypocholesterolemia increases the incidence and mortality of hemorrhagic stroke [34]. It is

Study or Subgroup	statin Events	statin Total	Control Events	Control Total	Weight (%)	Risk Ratio M-H, Fixed, 95% CI
Biffi 2011	109	238	267	461	28.7	0.79 [0.67, 0.93]
Eichel 2010	43	101	132	298	10.5	0.96 [0.74, 1.25]
FitzMaurice 2008	68	149	216	480	16.2	1.01 [0.83, 1.24]
Goldstein 2009	14	44	15	29	2.9	0.62 [0.35, 1.07]
Gomis 2010	9	34	77	235	3.1	0.81 [0.45, 1.46]
Leker 2009	19	89	66	223	5.9	0.72 [0 46, 1.13]
Mustanoja 2013	69	187	268	777	16.4	1.07 [0.87, 1.32]
Naval 2008	5	32	24	93	1.9	0.61 [0.25, 1.45]
Romero 2011	8	20	30	63	2.3	0.84 [0.46, 1.52]
Winkler 2013	39	190	86	236	12.1	0.56 [0.41, 0.78]
Total (95% CI)		*1084*		*2895*	*100.0*	*0.85 [0.78, 0.93]*
Total events	*383*		*1181*			

Heterogeneity: Chi² = 17.66, *df* = 9 (*P* = 0.04); I^2 = 49%
Test for overall effect: *Z* = 3.50 (*P* = 0.0005)

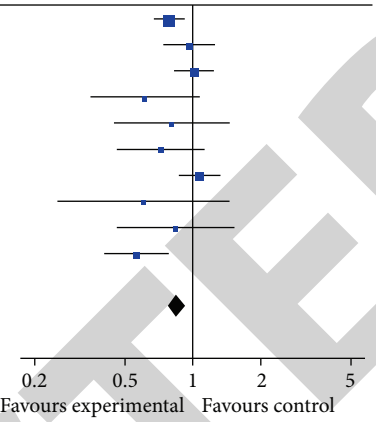

Figure 4: Meta-analyses of statin versus no-statin treatment in intracerebral hemorrhage after eliminating biased studies, comparing total mortality.

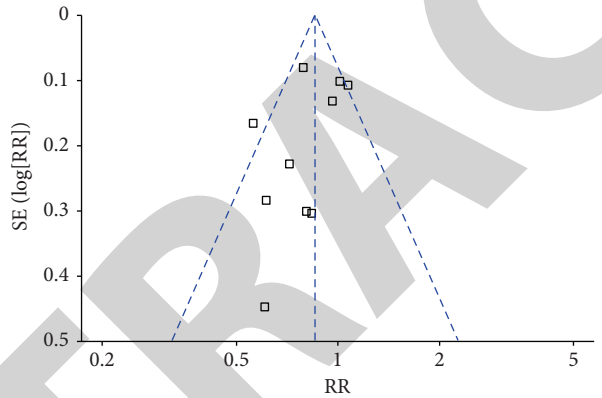

Figure 5: Funnel plot of the effect of statins on total mortality after intracerebral hemorrhage after eliminating biased studies.

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight (%)	Risk Ratio M-H, Random, 95% CI
Dowlatshahi 2012	190	537	663	1929	18.9	1.03 [0.90, 1.17]
Leker 2009	19	89	66	223	14.1	0.72 [0.46, 1.13]
Mustanoja 2013	43	187	186	777	16.7	0.96 [0.72, 1.28]
Ricard 2010	32	71	88	232	16.5	1.19 [0.88, 1.61]
Siddiqui 2017	89	1093	232	1364	17.7	0.48 [0.38, 0.60]
Winkler 2013	39	190	86	236	16.2	0.56 [0.41, 0.78]
Total (95% CI)		*2167*		*4761*	*100.0*	*0.79 [0.57, 1.08]*
Total events	*412*		*1321*			

Heterogeneity: Tau² = 0.13; Chi² = 45.45, *df* = 5 (*P* < 0.00001); I^2 = 89%
Test for overall effect: *Z* = 1.49 (*P* = 0.14)

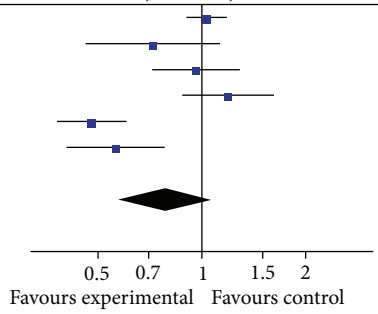

Figure 6: Meta-analyses of statin versus no-statin treatment in intracerebral hemorrhage, comparing in-hospital mortality.

speculated [35] that cholesterol is necessary for cerebrovascular wall integrity, and low cholesterol levels can increase the risk of cerebrovascular disease. Statins reduce plasma cholesterol levels, increase blood-brain barrier permeability, and inhibit platelet aggregation, thrombosis, and thrombin-linked reaction after acute ICH, resulting in further enlargement of cerebral hematoma and poor prognosis. Other studies [36] reported that statins had neuroprotective effects. Statins exert their pleiotropic function in various ways and have the ability to maintain the integrity of vascular endothelial cells, regulate the immune system and inhibit the inflammatory process. However, the results of these studies are contradictory [37], and the guidelines for cerebrovascular diseases [38] do not give clear

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight (%)	Risk Ratio M-H, Random, 95% CI
3.1.1 30-day mortality rate						
Dowlatshahi 2012	193	537	707	1929	9.1	0.98 [0.86, 1.11]
King 2012	92	292	302	1089	8.3	1.14 [0.94, 1.38]
Naval 2008	5	32	24	93	2.1	0.61 [0.25, 1.45]
Subtotal (95% CI)		*861*		*3111*	*19.5*	*1.02 [0.88, 1.19]*
Total events	*290*		*1033*			
Heterogeneity: Tau² = 0.01; Chi² = 2.91, *df* = 2 (*P* = 0.23); I^2 = 31%						
Test for overall effect: *Z* = 0.29 (*P* = 0.77)						
3.1.2 90-day mortality rate						
Biffi 2011	109	238	267	461	8.8	0.79 [0.67, 0.93]
Eichel 2010	43	101	132	298	7.4	0.96 [0.74, 1.25]
FitzMaurice 2008	68	149	216	480	8.2	1.01 [0.83, 1.24]
Goldstein 2009	14	44	15	29	3.9	0.62 [0.35, 1.07]
Gomis 2010	9	34	77	235	3.6	0.81 [0.45, 1.46]
Mustanoja 2013	63	187	237	777	7.9	1.10 [0.88, 1.39]
Pan 2014	12	220	630	2998	3.9	0.26 [0.15, 0.45]
Priglinger 2015	42	204	338	2980	7.0	1.82 [1.36, 2.42]
Romero 2011	8	20	30	63	3.6	0.84 [0.46, 1.52]
Siddiqui 2017	191	1093	355	1364	8.8	0.67 [0.57, 0.79]
Subtotal (95% CI)		*2290*		*9685*	*63.1*	*0.84 [0.67, 1.07]*
Total events	*559*		*2297*			
Heterogeneity: Tau² = 0.11; Chi² = 66.17, *df* = 9 (*P* < 0.00001); I^2 = 86%						
Test for overall effect: *Z* = 1.42 (*P* = 0.15)						
3.1.3 long-term mortality rate						
Dowlatshahi 2012	231	537	828	1929	9.3	1.00 [0.90, 1.12]
Mustanoja 2013	69	187	268	777	8.1	1.07 [0.87, 1.32]
Pan 2014	19	220	819	2998	0.0	0.32 [0.20, 0.49]
Winkler 2013	64	190	118	236	0.0	0.67 [0.53, 0.85]
Subtotal (95% CI)		*724*		*2706*	*17.4*	*1.02 [0.92, 1.12]*
Total events	*300*		*1096*			
Heterogeneity: Tau² = 0.00; Chi² = 0.29, *df* = 1 (*P* = 0.59); I^2 = 0%						
Test for overall effect: *Z* = 0.32 (*P* = 0.75)						
Total (95% CI)		*3875*		*15502*	*100.0*	*0.91 [0.79, 1.05]*
Total events	*1149*		*4426*			
Heterogeneity: Tau² = 0.05; Chi² = 77.44, *df* = 14 (*P* < 0.00001); I^2 = 82%						
Test for overall effect: *Z* = 1.24 (*P* = 0.21)						
Test for subgroup differences: Chi² = 2.21, *df* = 2 (*P* = 0.33), I^2 = 9.4%						

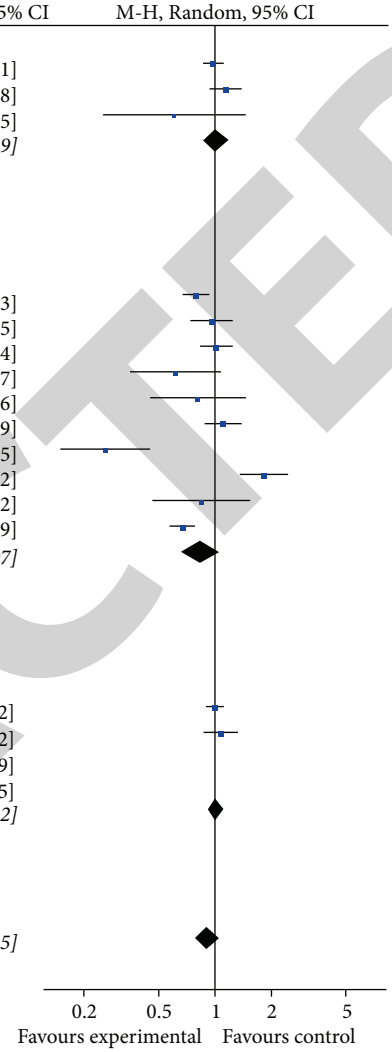

Figure 7: Meta-analyses of statin versus no-statin treatment in intracerebral hemorrhage, comparing 30 d, 90 d, or long-term mortality.

Study or Subgroup	statin Events	statin Total	Control Events	Control Total	Weight (%)	Risk Ratio M-H, Fixed, 95% CI
Biffi 2011	109	238	267	461	45.1	0.79 [0.67, 0.93]
Eichel 2010	43	101	132	298	16.6	0.96 [0.74, 1.25]
FitzMaurice 2008	68	149	216	480	25.4	1.01 [0.83, 1.24]
Goldstein 2009	14	44	15	29	4.5	0.62 [0.35, 1.07]
Gomis 2010	9	34	77	235	4.8	0.81 [0.45, 1.46]
Romero 2011	8	20	30	63	3.6	0.84 [0.46, 1.52]
Total (95% CI)		*586*		*1566*	*100.0*	*0.87 [0.78, 0.97]*
Total events	*251*		*737*			
Heterogeneity: Chi² = 5.75, *df* = 5 (*P* = 0.33); I^2 = 13%						
Test for overall effect: *Z* = 2.55 (*P* = 0.01)						

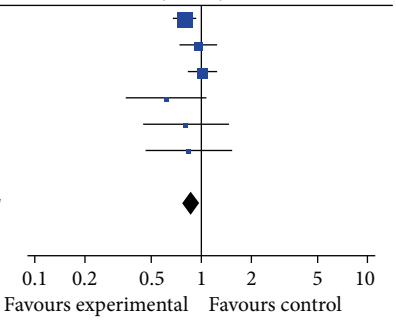

Figure 8: Meta-analyses of statin versus no-statin treatment in intracerebral hemorrhage after eliminating biased studies, comparing 90 d mortality.

Study or Subgroup	statin Events	statin Total	Control Events	Control Total	Weight (%)	Risk Ratio M-H, Random, 95% CI
Biffi 2011	60	238	87	461	8.9	1.34 [1.00, 1.78]
Dowlatshahi 2012	161	537	640	1929	11.1	0.90 [0.78, 1.04]
Eichel 2010	28	101	73	298	7.6	1.13 [0.78, 1.64]
Goldstein 2009	19	44	11	29	5.0	1.14 [0.64, 2.02]
Gomis 2010	21	34	99	235	8.7	1.47 [1.08, 1.99]
Leker 2009	45	89	69	223	9.0	1.63 [1.23, 2.17]
Mustanoja 2013	32	187	149	777	8.0	0.89 [0.63, 1.26]
Naval 2008	18	32	48	93	7.7	1.09 [0.76, 1.57]
Pan 2014	186	220	1868	2998	12.0	1.36 [1.27, 1.45]
Priglinger 2015	65	204	1428	2980	10.3	0.66 [0.54, 0.82]
Siddiqui 2017	581	1093	672	1364	11.8	1.08 [1.00, 1.17]
Total (95% CI)		*2779*		*11387*	*100.0*	*1.11 [0.94, 1.32]*
Total events	*1216*		*5144*			

Heterogeneity: Tau² = 0.06; Chi² = 97.10, *df* = 10 (*P* < 0.00001); I^2 = 90%
Test for overall effect: *Z* = 1.28 (*P* = 0.20)

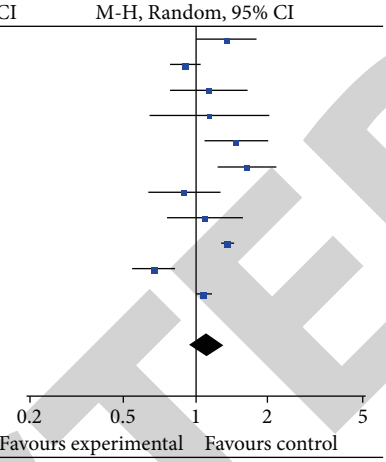

Figure 9: Meta-analyses of statin versus no-statin treatment in intracerebral hemorrhage, comparing total functional recovery.

Study or Subgroup	statin Events	statin Total	Control Events	Control Total	Weight (%)	Risk Ratio M-H, Fixed, 95% CI
Biffi 2011	60	238	87	461	6.9	1.34 [1.00, 1.78]
Eichel 2010	28	101	73	298	4.3	1.13 [0.78, 1.64]
Goldstein 2009	19	44	11	29	1.6	1.14 [0.64, 2.02]
Gomis 2010	21	34	99	235	2.9	1.47 [1.08, 1.99]
Leker 2009	45	89	69	223	4.6	1.63 [1.23, 2.17]
Mustanoja 2013	32	187	149	777	6.8	0.89 [0.63, 1.26]
Naval 2008	18	32	48	93	2.9	1.09 [0.76, 1.57]
Siddiqui 2017	581	1093	672	1364	70.0	1.08 [1.00, 1.17]
Total (95% CI)		*1818*		*3480*	*100.0*	*1.12 [1.05, 1.20]*
Total events	804		1208			

Heterogeneity: Chi² = 13.77, *df* = 7 (*P* = 0.06); I^2 = 49%
Test for overall effect: *Z* = 3.42 (*P* = 0.0006)

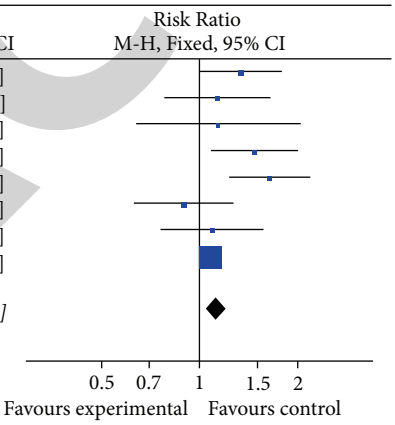

Figure 10: Meta-analyses of statin versus no-statin treatment in intracerebral hemorrhage after eliminating biased studies, comparing total functional recovery.

Study or Subgroup	statin Events	statin Total	Control Events	Control Total	Weight (%)	Risk Ratio M-H, Random, 95% CI
Dowlatshahi 2012	161	537	640	1929	30.4	0.90 [0.78, 1.04]
Leker 2009	45	89	69	223	25.1	1.63 [1.23, 2.17]
Mustanoja 2013	32	187	149	777	22.5	0.89 [0.63, 1.26]
Naval 2008	18	32	48	93	21.9	1.09 [0 76, 1.57]
Total (95% CI)		*845*		*3022*	*100.0*	*1.09 [0.81, 1.46]*
Total events	*256*		*906*			

Heterogeneity: Tau² = 0.07; Chi² = 14.19, *df* = 3 (*P* = 0.003); I^2 = 79%
Test for overall effect: *Z* = 0.57 (*P* = 0.57)

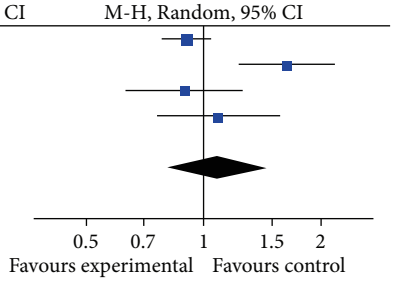

Figure 11: Meta-analyses of statin versus no-statin treatment in intracerebral hemorrhage, comparing functional recovery during hospitalization.

recommendations, which leads to conflicts between conventional secondary prevention and drug treatment for patients with previous ischemic cardiovascular and cerebrovascular diseases. Therefore, we conducted a meta-analysis on the mortality, functional prognosis, and other aspects of statins and intracerebral hemorrhage to further guide clinical treatment decisions.

Patients with ICH are always at risk of death, and the common causes of death are cerebral hernia, rebleeding, and related complications (such as pulmonary infection, gastrointestinal stress bleeding, and deep vein thrombosis). Statin is a common drug in the neurology department. In order to explore whether it can reduce the death rate after ICH, this study selected a number of studies for statistical

Study or Subgroup	Statin Events	Statin Total	Control Events	Control Total	Weight (%)	Risk Ratio M-H, Random, 95% CI
Eichel 2010	28	101	73	298	15.5	1.13 [0.78, 1.64]
Goldstein 2009	19	44	11	29	9.3	1.14 [0.64, 2.02]
Gomis 2010	21	34	99	235	18.4	1.47 [1.08, 1.99]
Pan 2014	187	220	1793	2998	28.6	1.42 [1.33, 1.51]
Siddiqui 2017	581	1093	672	1364	28.2	1.08 [1.00, 1.17]
Total (95% CI)		*1492*		*4924*	*100.0*	*1.25 [1.01, 1.55]*
Total events	*836*		*2648*			

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 40.03$, $df = 4$ ($P < 0.00001$); $I^2 = 90\%$
Test for overall effect: $Z = 2.05$ ($P = 0.04$)

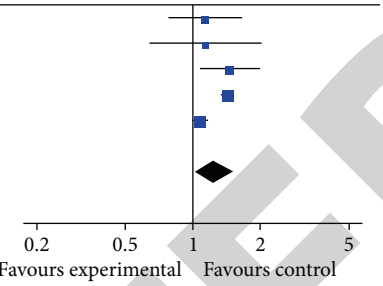

Figure 12: Meta-analyses of statin versus no-statin treatment in intracerebral hemorrhage, comparing 90 d functional recovery (a good functional prognosis was defined as MRS 0–3).

Study or Subgroup	Statin Events	Statin Total	Control Events	Control Total	Weight (%)	Risk Ratio M-H, Fixed, 95% CI
Eichel 2010	28	101	73	298	5.5	1.13 [0.78, 1.64]
Goldstein 2009	19	44	11	29	2.0	1.14 [0.64, 2.02]
Gomis 2010	21	34	99	235	3.7	1.47 [1.08, 1.99]
Siddiqui 2017	581	1093	672	1364	88.8	1.08 [1.00, 1.17]
Total (95% CI)		*1272*		*1926*	*100.0*	*1.10 [1.02, 1.18]*
Total events	*649*		*855*			

Heterogeneity: $Chi^2 = 3.71$, $df = 3$ ($P = 0.29$); $I^2 = 19\%$
Test for overall effect: $Z = 2.48$ ($P = 0.01$)

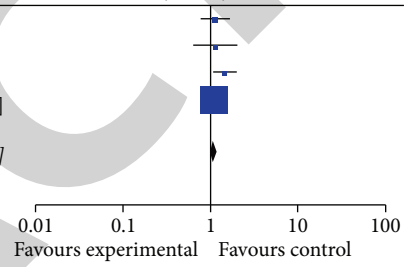

Figure 13: Meta-analyses of statin versus no-statin treatment in intracerebral hemorrhage after eliminating biased studies, comparing 90 d functional recovery (a good functional prognosis was defined as MRS 0–3).

Study or Subgroup	Statin Events	Statin Total	Control Events	Control Total	Weight (%)	Risk Ratio M-H, Random, 95% CI
Biffi 2011	60	238	87	461	15.2	1.34 [1.00, 1.78]
Eichel 2010	12	101	44	298	10.2	0.80 [0.44, 1.46]
Goldstein 2009	12	44	11	29	9.2	0.72 [0.37, 1.41]
Gomis 2010	17	34	78	235	13.7	1.51 [1.03, 2.21]
Pan 2014	164	220	1475	2998	17.7	1.52 [1.39, 1.65]
Priglinger 2015	65	204	1428	2980	16.5	0.66 [0.54, 0.82]
Siddiqui 2017	403	1093	481	1364	17.5	1.05 [0.94, 1.16]
Total (95% CI)		*1934*		*8365*	*100.0*	*1.06 [0.80, 1.42]*
Total events	*733*		*3604*			

Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 87.33$, $df = 6$ ($P < 0.00001$); $I^2 = 93\%$
Test for overall effect: $Z = 0.42$ ($P = 0.68$)

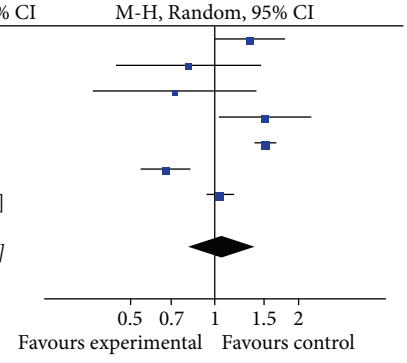

Figure 14: Meta-analyses of statin versus no-statin treatment in intracerebral hemorrhage, comparing 90 d functional recovery (a good functional prognosis was defined as MRS 0–2).

analysis of the death rate at each time after ICH as the evaluation index (during hospitalization, 30 d, 90 d, and long-term), and extracted binary variables. Preliminary analysis showed that there was high heterogeneity among studies of total mortality at various periods after ICH, and heterogeneity decreased after the studies by Priglinger and Pan were excluded from sensitivity analysis. The reason for the high heterogeneity of Pan et al.'s study [26] may be that Chinese people have a better understanding of the pharmacokinetics of statins and are better than Westerners in terms of absorption, distribution, and metabolism of statins [39]. The heterogeneity of Priglinger et al.'s study [27] was high because it explored whether lowering blood lipids secondary to statins increased the risk of spontaneous intracerebral hemorrhage. Most of the lipid-lowering drugs used were statins, and lipoprotein reduction was taken as the experimental group standard.

In this study, good functional prognosis in each period after ICH was selected as the evaluation index, and good functional recovery was defined as an MRS score of 0–3. Our results suggest that statins can indeed improve functional recovery after intracerebral hemorrhage, especially in the middle and long term, which is closely related to the enhancement of nerve repair and reduction of cerebral edema

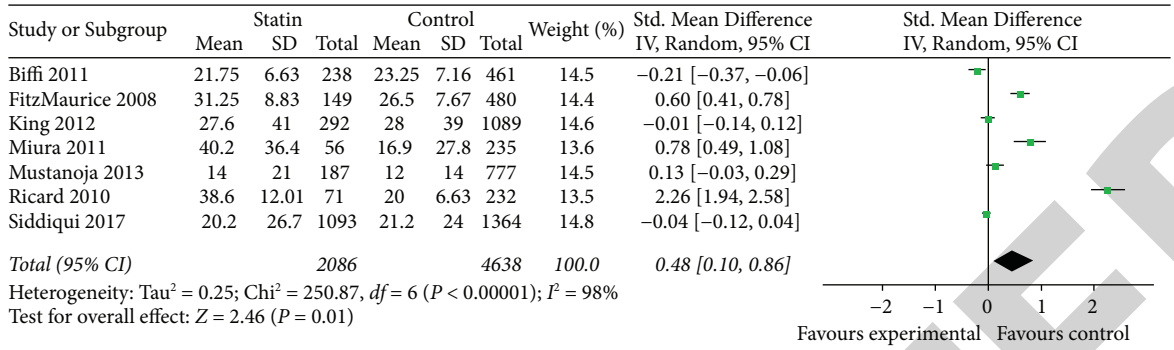

Figure 15: Meta-analyses of statin versus no-statin treatment in intracerebral hemorrhage, comparing hematoma formation.

by statins. After ICH occurred, cerebral vascular pressure caused by hematoma led to cerebral hypoperfusion, cerebral ischemia and hypoxia led to brain cell necrosis, enhanced brain free radical reaction, lipid peroxidation, and many other factors can lead to distant cellular brain edema. Statins may inhibit the formation of secondary cerebral edema in multiple ways due to their pleiotropism. Experimental studies [40] have shown that statins can resist thrombosis and fibrinolytic function (original activators inhibition of fibrinolytic enzyme inhibitors-1), in the acute phase, for example, statins can reduce the blood coagulation cascade and blood coagulation factor (organizational factor, V factor, and factor XIII), reduce the blood clot retraction, reducing the volume of hematoma surrounding edema. In rats, statins have also been shown to reduce the activation of glial cells and the release of cytokines such as interleukin and tumor necrosis factor, thereby achieving anti-inflammatory effects [41].

In our study, we evaluated that statins can reduce the total mortality after ICH, and improve the survival rate (90 d), without increasing the amount of hematoma.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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