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Association between non-HDLC and 1-year prognosis in patients with spontaneous intracerebral hemorrhage: a prospective cohort study

Journal:	BMJ Open
Manuscript ID	bmjopen-2022-061241
Article Type:	Original research
Date Submitted by the Author:	20-Jan-2022
Complete List of Authors:	Wang, Yu; Beijing Tiantan Hospital, Wu, Jianwei; Beijing Tiantan Hospital Wang, Anxin; Beijing Tiantan Hospital Jiang, Ruixuan; Beijing Tiantan Hospital, Department of neurology Wang, Wenjuan; Beijing Tiantan Hospital, Capital Medical University, Department of Neurology Zhao, Xingquan; Beijing Tiantan Hospital, Neurology
Keywords:	Stroke < NEUROLOGY, Lipid disorders < DIABETES & ENDOCRINOLOGY, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT





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Association between non-HDLC and 1-year prognosis in patients with

spontaneous intracerebral hemorrhage: a prospective cohort study

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Keywords: non-HDLC, intracerebral hemorrhage, prognosis, risk factors, mRS

Total number of tables and figures: 2 tables and 2 figures.

Word Count: 3847

ABSTRACT

Objectives: Previous studies suggested an inverse association between lipoprotein cholesterols and bleeding risk, while limited data was available about the predictive value of lipoproteins on intracerebral hemorrhage (ICH). Our recent research series showed that non-high-density lipoprotein cholesterol (non-HDLC) was an independent predictor of 3-month poor prognosis in ICH patients, we thus aimed to further investigate the association between non-HDLC levels and 1-year functional outcomes after ICH. **Design:** Prospective multicenter cohort study.

Setting: 13 hospitals in Beijing, China.

Participants: A total of 666 ICH patients were included between December 2014 and September 2016. **Methods:** Non-HDLC was calculated by subtracting HDL-C from TC. Patients were then grouped by non-HDLC levels into three categories: <3.4mmol/L, 3.4-4.2mmol/L, and \geq 4.2mmol/L. Both the univariate and multivariate logistic regressions were used to assess the association between non-HDLC levels and 1-year unfavorable functional outcomes (modified Rankin Scale \geq 3) in ICH patients. Moreover, sensitivity analysis was performed in ICH patients without statin use after admission.

Results: There were 33.5% (223/666) ICH patients identified with unfavorable functional outcomes at 1year follow-up. In the univariate analysis, patients who achieved non-HDLC levels above 4.2 mmol/L had a 49% decreased risk of 1-year poor prognosis (OR 0.51, 95% CI 0.33-0.81). However, non-HDLC did not retain its independent prognostic value in multivariate analysis, the fully adjusted OR values were 1.00 (reference), 0.99 (0.59-1.67), and 0.88 (0.48-1.62) from the lowest to the highest non-HDLC group Moreover, statin use after ICH onset made no difference to the long-term prognosis.

Conclusions: Non-HDLC was not an independent predictor for 1-year functional outcome in ICH patients, irrespective of post-stroke statin use. The predictive value of well-recognized confounding factors was

more dominant than non-HDLC on long-term prognosis.

Strengths and limitations of this study

• A multicenter, prospective, cohort study included 666 ICH patients from a total of 13 hospitals

in Beijing.

• Our study filled the vacancy about the association between non-HDLC and 1-year functional outcomes, simultaneously shed light on the diverse impacts of non-HDLC on short-term and long-term prognosis in ICH patients.

• Sensitivity analysis was performed to evaluate the association between non-HDLC and 1-year

functional outcomes in ICH patients with post-stroke statin use.

• Factors including radiological information or antithrombotic treatment may affect the results.

N.C.Z.O.J.L

INTRODUCTION

Intracerebral hemorrhage (ICH) is the second most common subtype of stroke, leading to severe disability and mortality.¹ Based on the nationally representative stroke survey in China published recently, ICH accounts for 25% of all strokes with an overall age-standardized incidence of 66.2 per 100,000 person-years.² Despite rapid advances in medicine, the management of ICH remains supportive without significant breakthroughs.³ Approximately 30-48% of ICH patients died within one month in low- to middle-income countries and only 12-39% of survivors could achieve long-term functional independence.^{1,4}

The conventional view on lipid-lowering targets goes "the lower, the better" in patients with atherosclerotic cardiovascular disease. However, previous epidemiology studies suggested an inverse association between lipoprotein cholesterols and ICH risk, hematoma expansion, and mortality.^{5, 6} Much remains to be discussed on the predictive value of lipoproteins on ICH. Our recent research series showed that low serum lipid levels were independent predictors of 3-month poor prognosis in ICH patients, and non-high-density lipoprotein cholesterol (non-HDLC) was the optimal parameter with high specificity.^{7, 8} However, the literature has scant information regarding the association between non-HDLC and long-term ICH prognosis.

We thus aimed to investigate the association between serum non-HDLC levels and 1-year functional outcomes after ICH in this prospective cohort study.

METHODS

Study population

The study was conducted in accordance with the Declaration of Helsinki and was approved by

the Institutional Review Board of the Beijing Tiantan Hospital (KY2014-023-02). All participants or their legal representatives provided written informed consent.

Our study is a multicenter, prospective, cohort study conducted in a total of 13 hospitals, evaluating the medical quality of cerebral hemorrhage on different etiologies in Beijing. From December 2014 to September 2016, 1964 consecutive ICH patients agreed to participate in the study. A total of 1881 patients met the following inclusion criteria: (1) aged 18 years or older, (2) had their first CT scan done within 72h after symptom onset. After excluding 159 secondary ICH patients (caused by trauma, tumor, aneurysm, arteriovenous malformation, coagulopathy, or other causes) and 20 patients diagnosed as primary ventricular hemorrhage, 1702 patients with primary intraparenchymal hemorrhage were included. Moreover, 294 patients underwent surgical procedures (including craniotomy hematoma removal, hematoma puncture, extraventricular drainage, and so on), 15 patients with anticoagulant therapy before symptom onset, 588 patients with missing data on the non-HDLC level, and 139 patients lost to follow-up at 1-year were excluded. Eventually, 666 patients with spontaneous ICH from 13 sites were included (Figure 1).

Baseline information

Demographic information including age, sex, onset to admission time, past medical history (including hypertension, diabetes mellitus, hyperlipidemia, cerebral infarction, and ICH), personal habits (including smoking and drinking status), and medication history (including antiplatelet and statin therapy) of each patient was collected using a standard questionnaire at baseline. Neurological deficits were assessed using the National Institute of Health Stroke Scale (NIHSS) Page 7 of 20

BMJ Open

and Glasgow Coma Scale (GCS) score by experienced neurologists on admission. Meanwhile, systolic and diastolic blood pressure (BP) were measured. A cranial CT scan was performed on admission and hematoma volume was then calculated as ABC/2 volumetric formula at each site.⁹ The location of hematoma was further subdivided into supratentorial and infratentorial regions.

Measurement of non-HDLC levels and other biochemical parameters

Blood samples were drawn from the antecubital vein the next morning after an overnight fast and analyzed within 4h. Total cholesterol (TC) was measured using the end-point test method and high-density lipoprotein cholesterol (HDL-C) was measured using a direct method. Non-HDLC was thus calculated by subtracting HDL-C from TC. Based on the National Lipid Association Recommendations,¹⁰ non-HDLC levels were categorized into five groups: desirable, <3.4mmol/L; above desirable, 3.4-4.2mmol/L; borderline high, 4.2-5.0mmol/L; high, 5.0-5.8 mmol/L; and very high, \geq 5.8 mmol/L. Accordingly, we integrated the last three groups into one group (\geq 4.2mmol/L) due to the limited number of patients.

For other biochemical parameters, random blood glucose was measured via the hexokinase/glucose-6-phosphate dehydrogenase method, serum creatinine was measured through rate reflectance spectrophotometry, white blood cell (WBC) together with platelet count were performed on EDTA with an ADVIA 120 counter (Siemens Healthcare Diagnostics, Saint-Denis, France).

Follow-up information and definition of 1-year ICH prognosis

Patients were followed up at 1-year after ICH onset via telephone interviews. Follow-up

evaluation was performed by neurologists who were blinded to prognostic factors. 1-year prognosis of patients was evaluated by modified Ranking Scale (mRS) score and categorized as favorable (mRS<3) and unfavorable functional outcome groups (mRS≥3).

Patient and public involvement

No patients were involved.

Statistical analysis

The patients were divided into three groups according to the clinical diagnosis of abnormal non-HDLC levels. Continuous variables were presented as median with interquartile range (IQR), categorical variables were described as count with percentage. The group differences of continuous variables were analyzed using ANOVA or Kruskal-Wallis test as appropriate, and for categorical variables, chi-squared tests were performed. Logistic regression was used to evaluate the association between non-HDLC levels and 1-year prognosis of ICH patients, with the lowest non-HDLC group (<3.4mmol/L) used as the reference. Both the univariate and multivariate analyses were conducted to estimate the odds ratios (ORs) and 95% confidence intervals (CIs). Multiple regression models were run as follows. Model 1 was adjusted for age and sex. Model 2 was adjusted for variates in model 1 plus history of ICH, glucose on admission, WBC on admission, baseline hematoma volume, hematoma location, time from onset to initial non-contrast CT, GCS score at admission, and systolic BP. *P*-values for trend were conducted using the three categories of non-HDLC as ordinal variables in the model. Additionally, sensitivity analysis was performed in ICH patients without statin use after admission (n=589). A 2-sided value of

p<0.05 was considered statistically significant. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

A total of 666 eligible patients were included, with a mean age of 59 years old (ranging from 51 to 68) and 69.1% (460/666) of them were males. Amongst them, 33.5% (223/666) were identified as 1-year poor outcomes, the proportion of which were 38.4%, 30.3%, and 24.2% from <3.4mmol/L group to \geq 4.2mmol/L group.

Baseline characteristics

There were significant differences in age, prior statin use, diastolic BP, glucose on admission, WBC on admission, and statin use after admission among the three categories of non-HDLC levels (p<0.05, Table 1). Those with higher lipid levels were more likely to be younger, not a prior statin user, having higher diastolic BP and glucose on admission.

Table 1. Baseline characteristics of participants according to non-HDLC levels.

	Tatal	non-HDLC levels			. .
	Total	<3.4mmol/L	3.4-4.2mmol/L	≥4.2mmol/L	– <i>P</i> -value
%)	666	359 (53.9)	175 (26.3)	132 (19.8)	
e, years	59 (51, 68)	61 (53, 70)	57 (49, 67)	54 (48 <i>,</i> 64)	<0.001
le, n (%)	460 (69.1)	258 (71.9)	120 (68.6)	82 (62.1)	0.116
set to admission time, h	4.0 (1.8, 11.9)	3.8 (1.7, 11.1)	4.0 (2.0, 11.0)	4.0 (1.8, 14.7)	0.840
Hypertension, n (%)	479 (71.9)	256 (71.3)	124 (70.9)	99 (75.0)	0.676
betes mellitus, n (%)	106 (15.9)	55 (15.3)	29 (16.6)	22 (16.7)	0.902
perlipidemia, n (%)	68 (10.2)	36 (10.0)	18 (10.3)	14 (10.6)	0.982
tory of Cl, n (%)	102 (15.3)	58 (16.2)	27 (15.4)	17 (12.9)	0.670
tory of ICH, n (%)	20 (3.0)	15 (4.2)	3 (1.7)	2 (1.5)	0.141
oking, n (%)	223 (33.5)	127 (35.4)	57 (32.6)	39 (29.6)	0.458
nking, n (%)	256 (38.4)	139 (38.7)	69 (39.4)	48 (36.4)	0.850
or antiplatelet use, n (%)	110 (16.5)	61 (17.0)	28 (16.0)	21 (15.9)	0.771
or statin use, n (%)	44 (6.6)	31 (8.6)	10 (5.7)	3 (2.3)	0.036
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1						
2 3		0 (2, 42)	0 (0, 45)	7 (2, 42)	E (2, 42)	0.000
4	NIHSS score on admission	8 (3, 13)	9 (3, 15)	7 (3, 13)	5 (2, 12)	0.083
5	GCS score on admission	14 (12, 15) 160 (149, 183)	14 (12, 15)	15 (13, 15)	15 (13, 15)	0.063 0.564
6	SBP on admission, mmHg DBP on admission, mmHg	95 (83, 105)	160 (150, 180) 92 (80, 102)	160 (145, 183) 96 (85, 106)	162 (150, 183) 97 (85, 109)	0.364 0.024
7	Glucose on admission, mmol/L	6.9 (5.9, 8.4)	6.6 (5.8, 8.1)	7.0 (5.9, 8.6)	7.1 (6.0, 9.3)	0.024
8	WBC on admission, 10 ⁹ /L	8.4 (6.6 <i>,</i> 10.9)	8.1 (6.3, 10.7)	9.1 (7.0, 11.7)	7.1 (6.0, 9.3)	0.032
9	Platelets on admission, 10 /L	212 (175, 252)	202 (164, 238)	218 (180, 259)	230 (192, 265)	<0.001
10	Creatinine on admission, μ mol/L	64.0 (53.0, 77.3)	64.6 (54.0, 76.4)	65.0 (52.3, 79.0)	62.0 (50.1, 76.0)	0.223
11	Statin use after admission, n (%)	77 (11.6)	19 (5.3)	30 (17.1)	28 (21.2)	<0.001
12 13	Infections, n (%)	136 (20.4)	77 (21.5)	39 (22.3)	20 (15.2)	0.239
14	Time from onset to initial NCCT, h	5.2 (2.3, 16.7)	5.2 (2.2, 14.8)	5.1 (2.3, 19.6)	4.8 (2.3, 19.4)	0.738
15	Baseline hematoma volume, ml	10.5 (5.0, 23.4)	10.7 (5.0, 25.0)	10.4 (5.5, 23.1)	10.0 (4.9, 16.8)	0.379
16	Hematoma location	2010 (010) 2011)	2017 (010) 2010)	2011 (010) 2012)		0.251
17	Supratentorial, n (%)	599 (89.7)	327 (91.2)	155 (88.2)	117 (87.5)	0.202
18	Infratentorial, n (%)	67 (10.3)	31 (8.8)	23 (11.8)	16 (12.5)	
19	ICH score	0 (0, 1)	0 (0, 1)	0 (0, 1)	0 (0, 1)	0.447
20	Values are (%) for cate					
21 22	Cl, cerebral infarction					
22	Scale; GCS, Glasgow		u			
24	-			ile, DDP, ulastolic	biobu pressure,	
25	WBC, white blood cell	s; NCCI, non-contra	st CI.			
26						
27						
28	Convolation hotoroom					
29 30	Correlation between	baseline non-HDLC a	and 1-year prognosi	s in ICH patients		
30 31						
32	In the univariate anal	ysis, higher non-HD	LC levels were signi	ificantly associated	with decreased	
33						
34	risk of 1-year poor ou	tcome (<i>p</i> =0.002). Pa	tients who achieved	I non-HDLC above 4	.2mmol/L had a	
35	<i>,</i> .	u ,			·	
36	49% lower risk of po	or functional outco	ma at 1 year (OB		191) While po	
37	45% lower fisk of po		ine at i year tok	0.51, 95% CI 0.554	5.61). While no	
38 39						
39 40	statistical difference v	vas retained after ad	djusting for age, sex	, and potential conf	ounding factors	
41						
42	(<i>p</i> >0.05). In the fully a	djusted model (Mo	del 2), the OR values	s were 1.00 (referer	nce), 0.99 (0.59-	
43						
44	1.67), and 0.88 (0.48	(-1.62) from the low	west to the highest	t non-HDIC group	Moreover the	
45	1.07), and 0.00 (0.40	1.02) Holli the lot	west to the highest		worcover, the	
46 47						
47 48	results maintained co	onsistency in sensiti	vity analysis among	g patients without	statin use after	
49						
50	admission (<i>p</i> =0.791, T	able 2).				
51						
52						
53						
54 55	Table 2. Odds ratios a	nd 95% Cl for 1 year	noor outcome (mpg	(3) according to p	on-HDIC lovals	
55 56		na 35% critir 1-yedi				

56						
57			non-HDLC levels		Continuous scolo	D for trond
58		<3.4mmol/L	3.4-4.2mmol/L	≥4.2mmol/L	Continuous scale	P for trend
59	1-year poor outcome, n (%)	138 (38.4)	53 (30.3)	32 (24.2)		
60	Univariate analysis	Ref.	0.70 (0.47, 1.02)	0.51 (0.33, 0.81)	0.71 (0.58, 0.88)	0.002
			9			

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2							
3	Multivaria	te analysis					
4	Model 1		Ref.	0.82 (0.54, 1.23)	0.66 (0.41, 1.06)	0.81 (0.65, 1.02)	0.075
5 6	Model 2		Ref.	0.99 (0.59, 1.67)	0.88 (0.48, 1.62)	0.95 (0.71, 1.27)	0.710
7	Sensitivity	analysis	Ref.	1.16 (0.67, 2.00)	0.86 (0.46, 1.62)	0.96 (0.71, 1.30)	0.791
8		Data are OR (95% Cl) ur	less otherwis	se stated.			
9		Model 1 adjusted for ag	ge and sex.				
10		Model 2 adjusted for	variates in m	odel 1 plus history	of ICH. glucose or	n admission. WBC on	
11		admission, baseline he			-		
12						onset to mittal non	
13 14		contrast CT, GCS score a					
14		Sensitivity analysis was			hout statin use afte	er admission (n=589),	
16		and adjusted for variate	es in model 2.				
17							
18							
19							
20		Notably, age, the histor	y of ICH, and	baseline hematom	a volume were posi	tively associated with	
21							
22 23		1-year poor prognosis i	n the multiva	ariate analysis. Whe	ereas, higher GCS so	ore at admission was	
23 24		, , , , , ,		,			
25		an independent predic	tor of favora	hla autromor Addi	tional datailed info	rmation was given in	
26				ble outcomes. Addi		iniation was given in	
27							
28		Figure 2.					
29							
30							
31 32							
33		DISCUSSION					
34		Discossion					
35							
36		This study provided e	vidence on	the association be	etween non-HDLC	evels and long-term	
37							
38		functional outcomes in	ICH patient	s. Although non-HD	DLC was a significar	nt 1-year predictor in	
39 40							
40 41		univariate analysis, it o	lid not retair	n its independent p	prognostic value in	multivariate analysis.	
42					ly in the		
43		Maraayar statin usa af	tor ICH oncot	mada na diffarance	to the long term a	rognosis	
44		Moreover, statin use af	ler ich onsei	indue no unierence	e to the long-term p		
45							
46		In our study, the prev	alence of 1	-year functional ind	dependence in ICH	patients was 66.5%	
47							
48 49		(443/666), far outweig	ghing the da	ata previously repo	orted. ⁴ According t	the inclusion and	
51		exclusion criteria, sever	e cases who	underwent surgical	treatment or lost t	o follow-up were not	
52				under went surgical			
53							
54		enrolled. It is noteworth	ny that per 1	mmol/L increment i	n non-HDLC yielded	a 29% decreased risk	
55							
56		of 1-year poor prognos	is (crude OR	0.71, 95% CI 0.58-0).88). However, cor	trary to our previous	
57 58							
58 59		research finding of the	independent	t role of non-HDLC	on short-term func	tional outcomes 7 the	
60		i cocaren mang or the	macpenaem				

results of this study showed that age, the history of ICH, baseline hematoma volume, admission GCS score, rather than non-HDLC level, were independent predictors for long-term functional outcomes in ICH patients. The validated predictors mentioned above kept high conformity with the items in ICH Functional Outcome Score, an effective prognostic model for 1-year poor functional outcomes after ICH,¹¹ whereas the absolute magnitude effect of low non-HDLC level on ICH prognosis was likely to be small and overshadowed with time.

It was reported that low levels of LDL-C and TC were associated with hematoma expansion.^{12, 13} As containing all the atherogenic lipoproteins, non-HDLC was served as the preferred target of lipid-lowering therapy.¹⁴ The potential mechanisms regarding the association between hypolipidemia and hematoma expansion, including impaired endothelial integrity,¹⁵ necrotic medial smooth muscle cells,¹⁶ increased erythrocyte fragility,¹⁷ inhibited platelet aggregation,¹⁸ and the resultant incident cerebral microbleeds.¹⁹ Despite the theoretical basis, our study failed to show an independent correlation between non-HDLC levels and 1-year functional outcomes in ICH patients. The secondary injury caused by low levels of lipoproteins in ICH patients was associated with short-term prognosis (30-day, 3-month),^{20, 21} while its impact on long-term prognosis (1-year) was negative, which merits further investigation due to the limited sample size and incomplete neuroimaging data on hematoma expansion in our study.

Statin treatment is another major concern,²² there were respectively 6.6% (44/666) and 11.6% (77/666) patients with pre- and post-stroke statin use in our study. Two recent meta-analyses concluded that there was no evidence to suggest pre-stroke statin therapy may increase bleeding risk in the context of ICH.^{23, 24} Whether to start, continue, or stop statin treatment in ICH patients has aroused great concern, we thus conducted a sensitivity analysis to evaluate the

effect of statin exposure after admission on ICH prognosis. No significant difference was detected between non-HDLC levels and 1-year prognosis in ICH patients in our study, irrespective of post-stroke statin use. A recent review indicated that statin should be applied after weighing the pros and cons given its pleiotropic as well as lipid-lowering effects.²⁵ Because of the relatively low stain exposure rate in our study, it is necessary to conduct randomized controlled trials around this topic.

Our study filled the vacancy about the association between non-HDLC and 1-year functional outcomes, simultaneously shed light on the diverse impacts of non-HDLC on short-term and long-term prognosis in ICH patients. Nonetheless, there are still some limitations. First, the follow-up radiological information was unavailable, which makes it difficult to verify the intermediate role of hematoma expansion between non-HDLC and poor prognosis. Secondly, medication therapy regarding antiplatelet or anticoagulation agents were not included in the multivariate analysis, whereas accumulating researches proved that antithrombotic treatment increased the risk of cerebral microbleeds as well as future ICH.^{26, 27} Although we collected pre-ictus antiplatelet use, restricted by the small sample size, further research is needed to provide insight into the relationship.

CONCLUSION

In conclusion, non-HDLC was not an independent predictor for 1-year functional outcome in ICH patients, irrespective of post-stroke statin use. The predictive value of well-recognized confounding factors was more dominant than non-HDLC on long-term poor prognosis. Further prospective studies are needed to assess the impact of lower non-HLDC levels on ICH prognosis.

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Contributors YW and JW performed the experiments, interpreted the results of statistical analysis, and drafted the manuscript. AW conducted the statistical analysis and interpreted the data. RJ and WW revised the manuscript for intellectual content. XZ had full access to all of the data and take responsibility for the integrity of the data and the accuracy of the data analysis.

Funding Our study was supported by grants from the Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences (2019-I2M-5-029), Beijing Natural Science Foundation (Z200016), Beijing Municipal Committee of Science and Technology (Z201100005620010), and Ministry of Science and Technology of the People's Republic of China (2018YFC1705003).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The study was approved by the Central Institutional Review Board of Beijing Tiantan Hospital (KY2014-023-02) and written informed consent was obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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Figure Legends

Figure 1. Flow chart for selection of study participants.

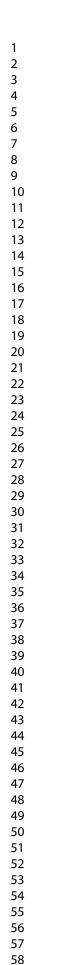
ICH, intracerebral hemorrhage; non-HDLC, non-high-density lipoprotein cholesterol.

Figure 2. Multivariate predictors of 1-year poor outcome among ICH patients.

Non-HDLC, non-high-density lipoprotein cholesterol; ICH, intracerebral hemorrhage; WBC, white

blood cells; NCCT, non-contrast CT; GCS, Glasgow Coma Scale; SBP, systolic blood pressure.

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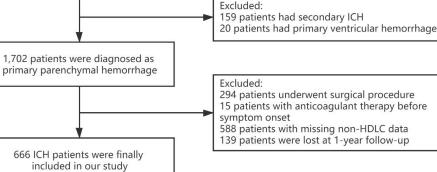
1,964 consecutive ICH patients were

prospectively included in the study

(2014.12~2016.09)

1,881 acute ICH patients aged over

18 years old



Excluded:

symptom onset

4 patients ≤18 years old

79 patients had their first CT scan over 72h after

Figure 1. Flow chart for selection of study participants. ICH, intracerebral hemorrhage; non-HDLC, non-high-density lipoprotein cholesterol.

146x108mm (220 x 220 DPI)

Variables	Poor outcome (mRS ≥3, n=178)	Odds ratio (95% Cl)
non-HDLC (vs ≤3.4mmol/L))		1
3.4-4.2mmol/L	0.99 (0.59, 1.67)	F+-1
≥4.2mmol/L	0.88 (0.48, 1.62)	F-
Age	1.08 (1.06, 1.10)	•
Male	0.83 (0.51, 1.35)	F 🔶 - 1
History of ICH	3.98 (1.32, 5.46)	⊢
Glucose on admission	1.02 (0.95, 1.10)	*
WBC on admission	1.01 (0.94, 1.09)	+
Platelet on admission	1.00 (0.99, 1.00)	+
Baseline hematoma volume	1.02 (1.01, 1.04)	+
Infratentorial hemorrhage	0.82 (0.37, 1.82)	⊢ ♦I
Time from onset to initial NCCT	0.99 (0.98, 1.01)	•
GCS score at admission	0.73 (0.66, 0.80)	34
SBP	1.00 (0.99, 1.00)	+
		1.0 2.0 4.0 6.0

Figure 2. Multivariate predictors of 1-year poor outcome among ICH patients. Non-HDLC, non-high-density lipoprotein cholesterol; ICH, intracerebral hemorrhage; WBC, white blood cells; NCCT, non-contrast CT; GCS, Glasgow Coma Scale; SBP, systolic blood pressure.

174x108mm (192 x 192 DPI)

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STROBE Statement—Checklist of items that should be included in reports of cohort studies

	Item No	Recommendation	Page No
Title and abstract	1	(<i>a</i>) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was	2
		done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of	5-6
-		recruitment, exposure, follow-up, and data collection	
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of	5,7
		participants. Describe methods of follow-up	
		(b) For matched studies, give matching criteria and number of exposed and	NA
		unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and	7
		effect modifiers. Give diagnostic criteria, if applicable	
Data sources/	8*	For each variable of interest, give sources of data and details of methods of	5-6
measurement		assessment (measurement). Describe comparability of assessment methods if	
		there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable,	7
		describe which groupings were chosen and why	7
Statistical methods	12	(<i>a</i>) Describe all statistical methods, including those used to control for confounding	7
		(b) Describe any methods used to examine subgroups and interactions	7
		(c) Explain how missing data were addressed	NA
		(d) If applicable, explain how loss to follow-up was addressed	NA
		(e) Describe any sensitivity analyses	7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially	5
1		eligible, examined for eligibility, confirmed eligible, included in the study,	
		completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social)	8
•		and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	5
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	8

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Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their	9-1	
		precision (eg, 95% confidence interval). Make clear which confounders were adjusted for		
		and why they were included		
		(b) Report category boundaries when continuous variables were categorized	9-3	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA	
Other analyses	er analyses 17 Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses			
Discussion				
Key results	18	Summarise key results with reference to study objectives	10	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision.	12	
		Discuss both direction and magnitude of any potential bias		
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations,	10	
		multiplicity of analyses, results from similar studies, and other relevant evidence	11	
Generalisability	21	Discuss the generalisability (external validity) of the study results	11	
Other informati	on			
Funding	22	Give the source of funding and the role of the funders for the present study and, if	13	
		applicable, for the original study on which the present article is based		

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Association between non-HDLC and 1-year prognosis in patients with spontaneous intracerebral hemorrhage: a prospective cohort study from 13 hospitals in Beijing

Journal:	BMJ Open
Manuscript ID	bmjopen-2022-061241.R1
Article Type:	Original research
Date Submitted by the Author:	15-Jul-2022
Complete List of Authors:	Wang, Yu; Beijing Tiantan Hospital, Wu, Jianwei; Beijing Tiantan Hospital Wang, Anxin; Beijing Tiantan Hospital Jiang, Ruixuan; Beijing Tiantan Hospital, Department of neurology Wang, Wenjuan; Beijing Tiantan Hospital, Department of Neurology Zhao, Xingquan; Beijing Tiantan Hospital, Neurology
Primary Subject Heading :	Neurology
Secondary Subject Heading:	Medical management
Keywords:	Stroke < NEUROLOGY, Lipid disorders < DIABETES & ENDOCRINOLOGY, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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Association between non-HDLC and 1-year prognosis in patients with spontaneous intracerebral

hemorrhage: a prospective cohort study from 13 hospitals in Beijing

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The authors declare that they have no conflicts of interest.

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Keywords: non-HDLC, intracerebral hemorrhage, prognosis, risk factors, mRS

Total number of tables and figures: 2 tables and 2 figures.

Word Count: 3573

ABSTRACT

Objectives: Previous studies suggested an inverse association between lipoprotein cholesterols and bleeding risk, while limited data was available about the predictive value of lipoproteins on intracerebral hemorrhage (ICH). Our recent research series showed that higher non-high-density lipoprotein cholesterol (non-HDLC) was an independent predictor of favourable 3-month outcome in ICH patients, we thus aimed to further investigate the association between non-HDLC levels and 1-year functional outcomes after ICH.

Design: Prospective multicenter cohort study.

Setting: 13 hospitals in Beijing, China.

Participants: A total of 666 ICH patients were included between December 2014 and September 2016. **Methods:** Non-HDLC was calculated by subtracting HDL-C from TC. Patients were then grouped by non-HDLC levels into three categories: <3.4mmol/L, 3.4-4.2mmol/L, and \geq 4.2mmol/L. Both the univariate and multivariate logistic regressions were used to assess the association between non-HDLC levels and 1-year unfavorable functional outcomes (modified Rankin Scale \geq 3) in ICH patients. Moreover, sensitivity analysis was performed in ICH patients without statin use after admission.

Results: There were 33.5% (223/666) ICH patients identified with unfavorable functional outcomes at 1year follow-up. In the univariate analysis, patients who achieved non-HDLC levels above 4.2 mmol/L had a 49% decreased risk of 1-year poor prognosis (OR 0.51, 95% CI 0.33-0.81). However, non-HDLC did not retain its independent prognostic value in multivariate analysis, the fully adjusted OR values were 1.00 (reference), 1.06 (0.63, 1.79), and 0.83 (0.45, 1.54) from the lowest to the highest non-HDLC group. Moreover, statin use after ICH onset made no difference to the long-term prognosis.

Conclusions: Non-HDLC was not an independent predictor for 1-year functional outcome in ICH patients,

irrespective of post-stroke statin use. The predictive value of well-recognized confounding factors was more dominant than non-HDLC on long-term prognosis.

Strengths and limitations of this study

• A multicenter, prospective, cohort study included 666 ICH patients from a total of 13 hospitals

in Beijing.

• Our study filled the vacancy about the association between non-HDLC and 1-year functional

outcomes, simultaneously shed light on the diverse impacts of non-HDLC on short-term and long-term

prognosis in ICH patients.

• Sensitivity analysis was performed to evaluate the association between non-HDLC and 1-year

functional outcomes in ICH patients with post-stroke statin use.

• Data regarding radiological information and antithrombotic treatment were unavailable,

further exploration is needed to verify our results.

INTRODUCTION

Intracerebral hemorrhage (ICH) is the second most common subtype of stroke, leading to severe disability and mortality.^[1] Based on the nationally representative stroke survey in China published recently, ICH accounts for 25% of all strokes with an overall age-standardized incidence of 66.2 per 100,000 person-years.^[2] Despite rapid advances in medicine, the management of ICH remains supportive without significant breakthroughs.^[3] Approximately 30-48% of ICH patients died within one month in low- to middle-income countries and only 12-39% of survivors could achieve long-term functional independence.^[1, 4]

The conventional view on lipid-lowering targets goes "the lower, the better" in patients with atherosclerotic cardiovascular disease. However, previous epidemiology studies suggested an inverse association between lipoprotein cholesterols and ICH risk, hematoma expansion, and mortality.^[5, 6] Much remains to be discussed on the predictive value of lipoproteins on ICH. Our recent research series showed that low serum lipid levels were independent predictors of 3-month poor prognosis in ICH patients, and non-high-density lipoprotein cholesterol (non-HDLC) was the optimal parameter with high specificity.^[7, 8] However, the literature has scant information regarding the association between non-HDLC and long-term ICH prognosis.

We thus aimed to investigate the association between serum non-HDLC levels and 1-year functional outcomes after ICH in this prospective cohort study.

METHODS

Study population

The study was conducted in accordance with the Declaration of Helsinki and was approved by

the Institutional Review Board of the Beijing Tiantan Hospital (KY2014-023-02). All participants or their legal representatives provided written informed consent.

Our study is a multicenter, prospective, cohort study conducted in a total of 13 hospitals, evaluating the medical quality of cerebral hemorrhage on different etiologies in Beijing. From December 2014 to September 2016, 1964 consecutive ICH patients agreed to participate in the study. A total of 1881 patients met the following inclusion criteria: (1) aged 18 years or older, (2) had their first CT scan done within 72h after symptom onset. After excluding 159 secondary ICH patients (caused by trauma, tumor, aneurysm, arteriovenous malformation, coagulopathy, or other causes) and 20 patients diagnosed as primary ventricular hemorrhage, 1702 patients with primary intraparenchymal hemorrhage were included. Moreover, 294 patients underwent surgical procedures (including craniotomy hematoma removal, hematoma puncture, extraventricular drainage, and so on), 15 patients with anticoagulant therapy before symptom onset, 588 patients with missing data on the non-HDLC level, and 139 patients lost to follow-up at 1-year were excluded. Eventually, 666 patients with spontaneous ICH from 13 sites were included (Figure 1).

Baseline information

 Demographic information including age, sex, onset to admission time, past medical history (including hypertension, diabetes mellitus, hyperlipidemia, cerebral infarction, and ICH), personal habits (including smoking and drinking status), and medication history (including antiplatelet and statin therapy) of each patient was collected using a standard questionnaire at baseline. Neurological deficits were assessed using the National Institute of Health Stroke Scale (NIHSS)

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and Glasgow Coma Scale (GCS) score by experienced neurologists on admission. Meanwhile, systolic and diastolic blood pressure (BP) were measured. A cranial CT scan was performed on admission and hematoma volume was then calculated as ABC/2 volumetric formula at each site.^[9] The location of hematoma was further subdivided into supratentorial and infratentorial regions. ICH score was calculated based on five parameters, GCS score, ICH volume, the presence of intraventricular extension, location of hematoma, and age.^[10]

Measurement of non-HDLC levels and other biochemical parameters

Blood samples were drawn from the antecubital vein the next morning after an overnight fast and analyzed within 4h. Total cholesterol (TC) was measured using the end-point test method and high-density lipoprotein cholesterol (HDL-C) was measured using a direct method. Non-HDLC was thus calculated by subtracting HDL-C from TC. Based on the National Lipid Association Recommendations,^[11] non-HDLC levels were categorized into five groups: desirable, <3.4mmol/L; above desirable, 3.4-4.2mmol/L; borderline high, 4.2-5.0mmol/L; high, 5.0-5.8 mmol/L; and very high, \geq 5.8 mmol/L. Accordingly, we integrated the last three groups into one group (\geq 4.2mmol/L) due to the limited number of patients.

For other biochemical parameters, random blood glucose was measured via the hexokinase/glucose-6-phosphate dehydrogenase method, serum creatinine was measured through rate reflectance spectrophotometry, white blood cell (WBC) together with platelet count were performed on EDTA with an ADVIA 120 counter (Siemens Healthcare Diagnostics, Saint-Denis, France).

Follow-up information and definition of 1-year ICH prognosis

Patients were followed up at 1-year after ICH onset via telephone interviews. Follow-up evaluation was performed by neurologists who were blinded to prognostic factors. 1-year prognosis of patients was evaluated by modified Ranking Scale (mRS) score and categorized as favorable (mRS<3) and unfavorable functional outcome groups (mRS≥3).

Patient and public involvement

No patients were involved.

Statistical analysis

The patients were divided into three groups according to the clinical diagnosis of abnormal non-HDLC levels. Continuous variables were presented as median with interquartile range (IQR), categorical variables were described as count with percentage. The group differences of continuous variables were analyzed using ANOVA or Kruskal-Wallis test as appropriate, and for categorical variables, chi-squared tests were performed. Logistic regression was used to evaluate the association between non-HDLC levels and 1-year prognosis of ICH patients, with the lowest non-HDLC group (<3.4mmol/L) used as the reference. Both the univariate and multivariate analyses were conducted to estimate the odds ratios (ORs) and 95% confidence intervals (CIs). Multiple regression models were run as follows. Model 1 was adjusted for age and sex. Model 2 was adjusted for variates in model 1 plus premorbid mRS score (<3 or \geq 3), history of ICH, glucose on admission, WBC on admission, baseline hematoma volume, hematoma location, time from onset to initial non-contrast CT, GCS score at admission, and systolic BP. *P*-values for trend were

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conducted using the three categories of non-HDLC as ordinal variables in the model. Additionally, sensitivity analysis was performed in ICH patients without statin use after admission (n=589). A 2-sided value of p<0.05 was considered statistically significant. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

A total of 666 eligible patients were included, with a mean age of 59 years old (ranging from 51 to 68) and 69.1% (460/666) of them were males. Amongst them, 33.5% (223/666) were identified as 1-year poor outcomes, the proportion of which were 38.4%, 30.3%, and 24.2% from <3.4mmol/L group to \geq 4.2mmol/L group.

Baseline characteristics

There were significant differences in age, prior statin use, diastolic BP, glucose on admission, WBC on admission, and statin use after admission among the three categories of non-HDLC levels (*p*<0.05, Table 1). Those with higher lipid levels were more likely to be younger, not a prior statin user, having higher diastolic BP and glucose on admission. While no statistical significance was observed in sex, premorbid mRS scale, onset to admission time, past medical history, personal habits, prior antiplatelet use, NIHSS score, GCS score, SBP, creatinine, infections, time from onset to initial NCCT, hematoma volume, hematoma location, and ICH score between the three groups.

 Table 1. Baseline characteristics of participants according to non-HDLC levels.

Takal		non-HDLC levels		D l
lotal	<3.4mmol/L	3.4-4.2mmol/L	≥4.2mmol/L	- <i>P</i> -value
666	359 (53.9)	175 (26.3)	132 (19.8)	
59 (51, 68)	61 (53, 70)	57 (49, 67)	54 (48 <i>,</i> 64)	<0.001
460 (69.1)	258 (71.9)	120 (68.6)	82 (62.1)	0.116
4.0 (1.8, 11.9)	3.8 (1.7, 11.1)	4.0 (2.0, 11.0)	4.0 (1.8, 14.7)	0.840
				0.614
643 (96.5)	345 (96.1)	171 (97.7)	127 (96.2)	
23 (3.5)	14 (3.9)	4 (2.3)	5 (3.8)	
479 (71.9)	256 (71.3)	124 (70.9)	99 (75.0)	0.676
106 (15.9)	55 (15.3)	29 (16.6)	22 (16.7)	0.902
68 (10.2)	36 (10.0)	18 (10.3)	14 (10.6)	0.982
102 (15.3)	58 (16.2)	27 (15.4)	17 (12.9)	0.670
20 (3.0)	15 (4.2)	3 (1.7)	2 (1.5)	0.141
223 (33.5)	127 (35.4)	57 (32.6)	39 (29.6)	0.458
256 (38.4)	139 (38.7)	69 (39.4)	48 (36.4)	0.850
110 (16.5)	61 (17.0)	28 (16.0)	21 (15.9)	0.771
44 (6.6)	31 (8.6)	10 (5.7)	3 (2.3)	0.036
8 (3, 13)	9 (3, 15)	7 (3, 13)	5 (2, 12)	0.083
14 (12, 15)	14 (12, 15)	15 (13, 15)	15 (13, 15)	0.063
160 (149, 183)	160 (150, 180)	160 (145, 183)	162 (150, 183)	0.564
95 (83, 105)	92 (80, 102)	96 (85, 106)	97 (85, 109)	0.024
6.9 (5.9, 8.4)	6.6 (5.8, 8.1)	7.0 (5.9, 8.6)	7.1 (6.0, 9.3)	0.032
8.4 (6.6, 10.9)	8.1 (6.3, 10.7)	9.1 (7.0, 11.7)	7.1 (6.0, 9.3)	0.007
212 (175, 252)	202 (164, 238)	218 (180, 259)	230 (192, 265)	<0.00
64.0 (53.0, 77.3)	64.6 (54.0, 76.4)	65.0 (52.3, 79.0)	62.0 (50.1, 76.0)	0.223
77 (11.6)	19 (5.3)	30 (17.1)	28 (21.2)	<0.00
136 (20.4)	77 (21.5)	39 (22.3)	20 (15.2)	0.239
5.2 (2.3, 16.7)		5.1 (2.3, 19.6)	4.8 (2.3, 19.4)	0.738
10.5 (5.0, 23.4)		10.4 (5.5, 23.1)		0.379
				0.251
599 (89.7)	327 (91.2)	155 (88.2)	117 (87.5)	
67 (10.3)		23 (11.8)		
			0 (0, 1)	0.447
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	-		•	
	$\begin{array}{c} 59 (51, 68) \\ 460 (69.1) \\ 4.0 (1.8, 11.9) \\ \hline \\ 643 (96.5) \\ 23 (3.5) \\ 479 (71.9) \\ 106 (15.9) \\ 68 (10.2) \\ 102 (15.3) \\ 20 (3.0) \\ 223 (33.5) \\ 256 (38.4) \\ 110 (16.5) \\ 44 (6.6) \\ 8 (3, 13) \\ 14 (12, 15) \\ 160 (149, 183) \\ 95 (83, 105) \\ 6.9 (5.9, 8.4) \\ 8.4 (6.6, 10.9) \\ 212 (175, 252) \\ 64.0 (53.0, 77.3) \\ 77 (11.6) \\ 136 (20.4) \\ 5.2 (2.3, 16.7) \\ 10.5 (5.0, 23.4) \\ \hline \\ 599 (89.7) \\ 67 (10.3) \\ 0 (0, 1) \\ \hline \\ egorical variables and \\ n Scale; Cl, cerebr \\ f Health Stroke Sc \end{array}$	<3.4mmol/L	Iotal $<3.4mmol/L$ $3.4-4.2mmol/L$ 666 $359(53.9)$ $175(26.3)$ 59(51, 68) $61(53, 70)$ $57(49, 67)$ 460(69.1) $258(71.9)$ $120(68.6)$ 4.0(1.8, 11.9) $3.8(1.7, 11.1)$ $4.0(2.0, 11.0)$ 643(96.5) $345(96.1)$ $171(97.7)$ 23(3.5) $14(3.9)$ $4(2.3)$ $479(71.9)$ $256(71.3)$ $124(70.9)$ 106(15.9) $55(15.3)$ $29(16.6)$ 68(10.2) $36(10.0)$ $18(10.3)$ 102(15.3) $58(16.2)$ $27(15.4)$ 20(3.0) $15(4.2)$ $3(1.7)$ 223(33.5) $127(35.4)$ $57(32.6)$ 256(38.4) $139(38.7)$ $69(39.4)$ 110(16.5) $61(17.0)$ $28(16.0)$ 44(6.6) $31(8.6)$ $10(5.7)$ 8(3, 13) $9(3, 15)$ $7(3, 13)$ 14(12, 15) $14(12, 15)$ $15(13, 15)$ 160(149, 183) $160(150, 180)$ $160(145, 183)$ 95(83, 105) $92(80, 102)$ $96(85, 106)$ 6.9(5.9, 8.4) $6.6(5.8, 8.1)$ $7.0(5.9, 8.6)$ 8.4(6.6, 10.9) $8.1(6.3, 10.7)$ $9.1(7.0, 11.7)$ 212(175, 252) $202(164, 238)$ $218(180, 259)$ $64.0(53.0, 77.3)$ $64.6(54.0, 76.4)$ $65.0(52.3, 79.0)$ $77(11.6)$ $19(5.3)$ $30(17.1)$ $136(20.4)$ $77(21.5)$ $39(22.3)$ $5.2(2.3, 16.7)$ $5.2(2.2, 14.8)$ $5.1(2.3, 19.6)$ $10.5(5.0, 23.4)$ $10.7(5.0, 25.0)$ $10.4(5.5, 23.1)$ $599(89.7)$ $327(91.2)$ $155(88.2)$ <td>Iotal<3.4mmol/L$3.4.4.2mmol/L$≥$4.2mmol/L$666359 (53.9)175 (26.3)132 (19.8)59 (51, 68)61 (53, 70)57 (49, 67)54 (48, 64)460 (69.1)258 (71.9)120 (68.6)82 (62.1)4.0 (1.8, 11.9)3.8 (1.7, 11.1)4.0 (2.0, 11.0)4.0 (1.8, 14.7)643 (96.5)345 (96.1)171 (97.7)127 (96.2)23 (3.5)14 (3.9)4 (2.3)5 (3.8)479 (71.9)256 (71.3)124 (70.9)99 (75.0)106 (15.9)55 (15.3)29 (16.6)22 (16.7)68 (10.2)36 (10.0)18 (10.3)14 (10.6)102 (15.3)58 (16.2)27 (15.4)17 (12.9)20 (3.0)15 (4.2)3 (1.7)2 (1.5)223 (33.5)127 (35.4)57 (32.6)39 (29.6)256 (38.4)139 (38.7)69 (39.4)48 (36.4)110 (16.5)61 (17.0)28 (16.0)21 (15.9)44 (6.6)31 (8.6)10 (5.7)3 (2.3)8 (3, 13)9 (3, 15)7 (3, 13)5 (2, 12)14 (12, 15)15 (13, 15)15 (13, 15)160 (149, 183)160 (150, 180)160 (145, 183)95 (83, 105)92 (80, 102)96 (85, 106)97 (85, 109)6.9 (5.9, 8.4)6.6 (5.8, 8.1)7.0 (5.9, 8.6)7.1 (6.0, 9.3)212 (175, 252)202 (164, 238)218 (180, 259)230 (192, 265)64.0 (53.0, 77.3)64.6 (54.0, 76.4)65.0 (52.3, 79.0)62.0 (50.1, 76.0)77 (11.6)19 (5.3)30 (17.1)28 (21.2</td>	Iotal<3.4mmol/L $3.4.4.2mmol/L$ ≥ $4.2mmol/L$ 666359 (53.9)175 (26.3)132 (19.8)59 (51, 68)61 (53, 70)57 (49, 67)54 (48, 64)460 (69.1)258 (71.9)120 (68.6)82 (62.1)4.0 (1.8, 11.9)3.8 (1.7, 11.1)4.0 (2.0, 11.0)4.0 (1.8, 14.7)643 (96.5)345 (96.1)171 (97.7)127 (96.2)23 (3.5)14 (3.9)4 (2.3)5 (3.8)479 (71.9)256 (71.3)124 (70.9)99 (75.0)106 (15.9)55 (15.3)29 (16.6)22 (16.7)68 (10.2)36 (10.0)18 (10.3)14 (10.6)102 (15.3)58 (16.2)27 (15.4)17 (12.9)20 (3.0)15 (4.2)3 (1.7)2 (1.5)223 (33.5)127 (35.4)57 (32.6)39 (29.6)256 (38.4)139 (38.7)69 (39.4)48 (36.4)110 (16.5)61 (17.0)28 (16.0)21 (15.9)44 (6.6)31 (8.6)10 (5.7)3 (2.3)8 (3, 13)9 (3, 15)7 (3, 13)5 (2, 12)14 (12, 15)15 (13, 15)15 (13, 15)160 (149, 183)160 (150, 180)160 (145, 183)95 (83, 105)92 (80, 102)96 (85, 106)97 (85, 109)6.9 (5.9, 8.4)6.6 (5.8, 8.1)7.0 (5.9, 8.6)7.1 (6.0, 9.3)212 (175, 252)202 (164, 238)218 (180, 259)230 (192, 265)64.0 (53.0, 77.3)64.6 (54.0, 76.4)65.0 (52.3, 79.0)62.0 (50.1, 76.0)77 (11.6)19 (5.3)30 (17.1)28 (21.2

Correlation between baseline non-HDLC and 1-year prognosis in ICH patients

pressure; DBP, diastolic blood pressure; WBC, white blood cells; NCCT, non-contrast CT.

In the univariate analysis, higher non-HDLC levels were significantly associated with decreased risk of 1-year poor outcome (*p*=0.002). Patients who achieved non-HDLC above 4.2mmol/L had a 49% lower risk of poor functional outcome at 1 year (OR 0.51, 95% CI 0.33-0.81). While no statistical difference was retained after adjusting for age, sex, and potential confounding factors

(p>0.05). In the fully adjusted model (Model 2), the OR values were 1.00 (reference), 1.06 (0.63, 1.79), and 0.83 (0.45, 1.54) from the lowest to the highest non-HDLC group. Moreover, the results maintained consistency in sensitivity analysis among patients without statin use after admission (p=0.842, Table 2).

Table 2. Odds ratios and 95% CI for 1-year poor outcome (mRS ≥3) according to non-HDLC levels.

			non-HDLC levels		- Continuous scale	P for tren
		<3.4mmol/L	3.4-4.2mmol/L	≥4.2mmol/L	continuous scale	7 101 11 11
1-year poor ou		138 (38.4)	53 (30.3)	32 (24.2)		
Univariate ana	alysis	Ref.	0.70 (0.47, 1.02)	0.51 (0.33, 0.81)	0.71 (0.58, 0.88)	0.002
Multivariate a	nalysis					
Model 1		Ref.	0.82 (0.54, 1.23)	0.66 (0.41, 1.06)	0.81 (0.65, 1.02)	0.075
Model 2		Ref.	1.06 (0.63, 1.79)	0.83 (0.45, 1.54)	0.89 (0.76, 1.05)	0.694
Sensitivity ana	alysis	Ref.	0.92 (0.53, 1.61)	1.12 (0.58, 2.16)	0.92 (0.78, 1.08)	0.842
Da	ta are OR (95% C	CI) unless otherw	ise stated.			
Mo	odel 1 adjusted f	or age and sex.				
Мс	odel 2 adjusted	for variates in m	nodel 1 plus premor	bid mRS score (<3	or ≥3), history of IC	Н,
glu	cose on admissi	on, WBC on adm	ission, baseline hem	atoma volume, her	natoma location, tin	ne
fro	m onset to initia	I non-contrast C	T, GCS score at admis	ssion, systolic blood	pressure.	
Ser	nsitivity analysis	was performed	in ICH patients wit	hout statin use aft	er admission (n=589)).
		riates in model 2	· · · · · · ·			·)
and	u aujusteu for va	nates in model 2	<u>.</u> .			
No	tably, age, prem	iorbid mRS score	e (<3 or ≥3), and bas	seline hematoma v	olume were positive	ly
ass	ociated with 1-y	ear poor progno	sis in the multivaria	te analysis. Wherea	s, higher GCS score	at
be	mission was an i	ndependent pro	dictor of favorable o	utcomes Additions	l detailed informatio	n
aui				accornes. Additiona		711
wa	s given in Figure	2.				
DIS	SCUSSION					
Thi	is study provide	ed evidence on	the association be	etween non-HDLC	levels and long-ter	m
fur	octional outcome	es in ICH nation	ts. Although non-HE	IC was a significa	nt 1-vear predictor	in
Tur						

univariate analysis, it did not retain its independent prognostic value in multivariate analysis. Moreover, statin use after ICH onset made no difference to the long-term prognosis.

In our study, the prevalence of 1-year functional independence in ICH patients was 66.5% (443/666), far outweighing the data previously reported.^[4] According to the inclusion and exclusion criteria, severe cases who underwent surgical treatment or lost to follow-up were not enrolled. It is noteworthy that per 1 mmol/L increment in non-HDLC yielded a 29% decreased risk of 1-year poor prognosis (crude OR 0.71, 95% CI 0.58-0.88). However, contrary to our previous research finding of the independent role of non-HDLC on short-term functional outcomes,^[7] the results of this study showed that age, premorbid mRS score, baseline hematoma volume, admission GCS score, rather than non-HDLC level, were independent predictors for long-term functional outcomes in ICH patients. The validated predictors mentioned above kept high conformity with the items in ICH Functional Outcome Score, an effective prognostic model for 1-year poor functional outcomes after ICH,^[12] whereas the absolute magnitude effect of low non-HDLC level on ICH prognosis was likely to be small and overshadowed with time. Beyond that, the amount of rehabilitation with functional gains might also related.^[13]

It was reported that low levels of LDL-C and TC were associated with hematoma expansion.^[14, 15] As containing all the atherogenic lipoproteins, non-HDLC was served as the preferred target of lipid-lowering therapy.^[16] The potential mechanisms regarding the association between hypolipidemia and hematoma expansion, including impaired endothelial integrity,^[17] necrotic medial smooth muscle cells,^[18] increased erythrocyte fragility,^[19] inhibited platelet aggregation,^[20] and the resultant incident cerebral microbleeds.^[21] Despite the theoretical basis, our study failed to show an independent correlation between non-HDLC levels and 1-year

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functional outcomes in ICH patients. The secondary injury caused by low levels of lipoproteins in ICH patients was associated with short-term prognosis (30-day, 3-month),^[22, 23] while its impact on long-term prognosis (1-year) was negative, which merits further investigation due to the limited sample size and incomplete neuroimaging data on hematoma expansion in our study. Statin treatment is another major concern,^[24] there were respectively 6.6% (44/666) and 11.6% (77/666) patients with pre- and post-stroke statin use in our study. Two recent meta-analyses concluded that there was no evidence to suggest pre-stroke statin therapy may increase bleeding risk in the context of ICH.^[25, 26] Whether to start, continue, or stop statin treatment in ICH patients has aroused great concern, we thus conducted a sensitivity analysis to evaluate the effect of statin exposure after admission on ICH prognosis. No significant difference was detected between non-HDLC levels and 1-year prognosis in ICH patients in our study, irrespective of post-stroke statin use. A recent review indicated that statin should be applied after weighing the pros and cons given its pleiotropic as well as lipid-lowering effects.^[27] Because of the relatively low stain exposure rate in our study, it is necessary to conduct randomized controlled trials around this topic.

Our study filled the vacancy about the association between non-HDLC and 1-year functional outcomes, simultaneously shed light on the diverse impacts of non-HDLC on short-term and long-term prognosis in ICH patients. Nonetheless, there are still some limitations. First, the follow-up radiological information was unavailable, which makes it difficult to verify the intermediate role of hematoma expansion between non-HDLC and poor prognosis. Secondly, ICH caused by cerebral amyloid angiopathy has a higher rebleeding risk than hypertensive one,^[28] while data regarding the cause of ICH was not documented in our study. Despite no correlation

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was observed between the history of ICH and 1-year functional outcome, the impact of ICH etiology merits further investigation. Thirdly, medication therapy regarding antiplatelet or anticoagulation agents were not included in the multivariate analysis, whereas accumulating researches proved that antithrombotic treatment increased the risk of cerebral microbleeds as well as future ICH.^[29, 30] Although we collected pre-ictus antiplatelet use, restricted by the small sample size, further research is needed to provide insight into the relationship. Moreover, since our study based on a highly selected population with small hematoma and relatively good neurologic status to achieve precise research, the findings cannot be generalized to the whole ICH population.

CONCLUSION

In conclusion, non-HDLC was not an independent predictor for 1-year functional outcome in ICH patients, irrespective of post-stroke statin use. The predictive value of well-recognized confounding factors was more dominant than non-HDLC on long-term poor prognosis. Further prospective studies are needed to assess the impact of lower non-HLDC levels on ICH prognosis.

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Contributors YW and JW performed the experiments, interpreted the results of statistical analysis, and drafted the manuscript. AW conducted the statistical analysis and interpreted the data. RJ revised the manuscript for intellectual content. WW and XZ had full access to all of the data and take responsibility for the integrity of the data and the accuracy of the data analysis.

Funding Our study was supported by grants from the Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences (2019-I2M-5-029), Beijing Natural Science Foundation (Z200016), Beijing Municipal Committee of Science and Technology (Z201100005620010), and Ministry of Science and Technology of the People's Republic of China (2018YFC1705003).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The study was approved by the Central Institutional Review Board of Beijing Tiantan Hospital (KY2014-023-02) and written informed consent was obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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Figure Legends

Figure 1. Flow chart for selection of study participants.

ICH, intracerebral hemorrhage; non-HDLC, non-high-density lipoprotein cholesterol.

Figure 2. Multivariate predictors of 1-year poor outcome among ICH patients.

Non-HDLC, non-high-density lipoprotein cholesterol; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; WBC, white blood cells; NCCT, non-contrast CT; GCS, Glasgow Coma Scale; SBP, systolic blood pressure.

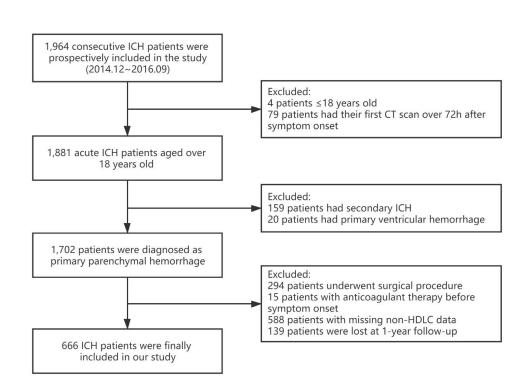


Figure 1. Flow chart for selection of study participants. ICH, intracerebral hemorrhage; non-HDLC, non-high-density lipoprotein cholesterol. BMJ Open: first published as 10.1136/bmjopen-2022-061241 on 2 November 2022. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright

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Variables	Poor outcome (mRS ≥3, n=178)	Odds ratio (95% CI)
non-HDLC (vs <3.4mmol/L)		
3.4-4.2mmol/L	1.06 (0.63, 1.79)	La L
≥4.2mmol/L	0.83 (0.45, 1.54)	⊢ ♣—1
Age, years	1.08 (1.06, 1.10)	•
Male	0.84 (0.52, 1.36)	F#-1
Premorbid mRS score ≥3	3.89 (1.43, 6.77)	⊢ ⊢ ⊢ ⊢
History of ICH	2.80 (0.95, 5.27)	↓ → → → →
Glucose on admission, mmol/L	1.02 (0.95, 1.11)	
WBC on admission, 10E9/L	1.00 (0.93, 1.08)	
Platelet on admission, 10E9/L	1.00 (0.99, 1.00)	+
Baseline hematoma volume, mL	1.02 (1.01, 1.04)	+
Infratentorial hemorrhage	0.82 (0.37, 1.82)	F#1
Tme from onset to initial NCCT, hours	0.99 (0.98, 1.01)	•
GCS score on admission	0.73 (0.66, 0.80)	*
SBP, mmHg	0.99 (0.99, 1.00)	•
		1.0 2.0 4.0 6.0

Figure 2. Multivariate predictors of 1-year poor outcome among ICH patients.

Non-HDLC, non-high-density lipoprotein cholesterol; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; WBC, white blood cells; NCCT, non-contrast CT; GCS, Glasgow Coma Scale; SBP, systolic blood pressure.

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STROBE Statement—Checklist of items that should be included in reports of cohort studies

	Item No	Recommendation	Pag No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the	1
		abstract	
		(b) Provide in the abstract an informative and balanced summary of what was	2
		done and what was found	
Introduction			1
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of	5-6
Setting		recruitment, exposure, follow-up, and data collection	
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of	5,7
i articipants	0	participants. Describe methods of follow-up	
		(b) For matched studies, give matching criteria and number of exposed and	NA
		unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and	7
v artables	/	effect modifiers. Give diagnostic criteria, if applicable	
Data sources/	8*	For each variable of interest, give sources of data and details of methods of	5-6
measurement	0	assessment (measurement). Describe comparability of assessment methods if	
medsurement		there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable,	7
Qualificative variables		describe which groupings were chosen and why	
Statistical methods	12	(<i>a</i>) Describe all statistical methods, including those used to control for	7
		confounding	
		(b) Describe any methods used to examine subgroups and interactions	7
		(c) Explain how missing data were addressed	NA
		(d) If applicable, explain how loss to follow-up was addressed	NA
		(<i>e</i>) Describe any sensitivity analyses	7
Descrites			
Results Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially	5
Farticipants	13.	eligible, examined for eligibility, confirmed eligible, included in the study,	
		completing follow-up, and analysed	
			5
		(b) Give reasons for non-participation at each stage(c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social)	8
Descriptive uata	14'		
		and information on exposures and potential confounders	5
		(b) Indicate number of norticinante with missing deta for each veriable of interest	
		(b) Indicate number of participants with missing data for each variable of interest(c) Summarise follow-up time (eg, average and total amount)	NA

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Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their	9-10
		precision (eg, 95% confidence interval). Make clear which confounders were adjusted for	
		and why they were included	
		(b) Report category boundaries when continuous variables were categorized	9-10
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a	NA
		meaningful time period	
Other analyses	17	Report other analyses done-eg analyses of subgroups and interactions, and sensitivity	9
		analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision.	12
		Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations,	10-
		multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other informati	on		
Funding	22	Give the source of funding and the role of the funders for the present study and, if	13
		applicable, for the original study on which the present article is based	

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Association between non-HDLC and 1-year prognosis in patients with spontaneous intracerebral hemorrhage: a prospective cohort study from 13 hospitals in Beijing

Journal:	BMJ Open
Manuscript ID	bmjopen-2022-061241.R2
Article Type:	Original research
Date Submitted by the Author:	06-Sep-2022
Complete List of Authors:	Wang, Yu; Beijing Tiantan Hospital, Wu, Jianwei; Beijing Tiantan Hospital Wang, Anxin; Beijing Tiantan Hospital Jiang, Ruixuan; Beijing Tiantan Hospital, Department of neurology Wang, Wenjuan; Beijing Tiantan Hospital, Department of Neurology Zhao, Xingquan; Beijing Tiantan Hospital, Neurology
Primary Subject Heading :	Neurology
Secondary Subject Heading:	Medical management
Keywords:	Stroke < NEUROLOGY, Lipid disorders < DIABETES & ENDOCRINOLOGY, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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Association between non-HDLC and 1-year prognosis in patients with spontaneous intracerebral

hemorrhage: a prospective cohort study from 13 hospitals in Beijing

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The authors declare that they have no conflicts of interest.

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Keywords: non-HDLC, intracerebral hemorrhage, prognosis, risk factors, mRS

Total number of tables and figures: 2 tables and 2 figures.

Word Count: 3956

ABSTRACT

Objectives: Previous studies suggested an inverse association between lipoprotein cholesterols and bleeding risk, while limited data was available about the predictive value of lipoproteins on intracerebral hemorrhage (ICH). Our recent research series showed that higher non-high-density lipoprotein cholesterol (non-HDLC) was an independent predictor of favourable 3-month outcome in ICH patients, we thus aimed to further investigate the association between non-HDLC levels and 1-year functional outcomes after ICH.

Design: Prospective multicenter cohort study.

Setting: 13 hospitals in Beijing, China.

Participants: A total of 666 ICH patients were included between December 2014 and September 2016. **Methods:** Non-HDLC was calculated by subtracting HDL-C from TC. Patients were then grouped by non-HDLC levels into three categories: <3.4mmol/L, 3.4-4.2mmol/L, and \geq 4.2mmol/L. Both the univariate and multivariate logistic regressions were used to assess the association between non-HDLC levels and 1-year unfavorable functional outcomes (modified Rankin Scale \geq 3) in ICH patients. Moreover, sensitivity analysis was performed in ICH patients without statin use after admission.

Results: There were 33.5% (223/666) ICH patients identified with unfavorable functional outcomes at 1year follow-up. In the univariate analysis, patients who achieved non-HDLC levels above 4.2 mmol/L had a 49% decreased risk of 1-year poor prognosis (OR 0.51, 95% CI 0.33-0.81). However, non-HDLC did not retain its independent prognostic value in multivariate analysis, the fully adjusted OR values were 1.00 (reference), 1.06 (0.63, 1.79), and 0.83 (0.45, 1.54) from the lowest to the highest non-HDLC group. Moreover, statin use after ICH onset made no difference to the long-term prognosis.

Conclusions: Non-HDLC was not an independent predictor for 1-year functional outcome in ICH patients,

irrespective of post-stroke statin use. The predictive value of well-recognized confounding factors was more dominant than non-HDLC on long-term prognosis.

Strengths and limitations of this study

• A multicenter, prospective, cohort study included 666 ICH patients from a total of 13 hospitals

in Beijing.

• Our study filled the vacancy about the association between non-HDLC and 1-year functional

outcomes, simultaneously shed light on the diverse impacts of non-HDLC on short-term and long-term

prognosis in ICH patients.

• Sensitivity analysis was performed to evaluate the association between non-HDLC and 1-year

functional outcomes in ICH patients with post-stroke statin use.

• Data regarding hematoma expansion and antithrombotic treatment were unavailable, further

exploration is needed to verify our results.

INTRODUCTION

Intracerebral hemorrhage (ICH) is the second most common subtype of stroke, leading to severe disability and mortality.^[1] Based on the nationally representative stroke survey in China published recently, ICH accounts for 25% of all strokes with an overall age-standardized incidence of 66.2 per 100,000 person-years.^[2] Despite rapid advances in medicine, the management of ICH remains supportive without significant breakthroughs.^[3] Approximately 30-48% of ICH patients died within one month in low- to middle-income countries and only 12-39% of survivors could achieve long-term functional independence.^[1, 4]

The conventional view on lipid-lowering targets goes "the lower, the better" in patients with atherosclerotic cardiovascular disease. However, previous epidemiology studies suggested an inverse association between lipoprotein cholesterols and ICH risk, hematoma expansion, and mortality.^[5, 6] Much remains to be discussed on the predictive value of lipoproteins on ICH. Our recent research series showed that low serum lipid levels were independent predictors of 3-month poor prognosis in ICH patients, and non-high-density lipoprotein cholesterol (non-HDLC) was the optimal parameter with high specificity.^[7, 8] However, the literature has scant information regarding the association between non-HDLC and long-term ICH prognosis.

We thus aimed to investigate the association between serum non-HDLC levels and 1-year functional outcomes after ICH in this prospective cohort study.

METHODS

Study population

The study was conducted in accordance with the Declaration of Helsinki and was approved by

the Institutional Review Board of the Beijing Tiantan Hospital (KY2014-023-02). All participants or their legal representatives provided written informed consent.

Our study is a multicenter, prospective, cohort study conducted in a total of 13 hospitals, evaluating the medical quality of cerebral hemorrhage on different etiologies in Beijing. From December 2014 to September 2016, 1964 consecutive ICH patients agreed to participate in the study. A total of 1881 patients met the following inclusion criteria: (1) aged 18 years or older, (2) had their first CT scan done within 72h after symptom onset. After excluding 159 secondary ICH patients (caused by trauma, tumor, aneurysm, arteriovenous malformation, coagulopathy, or other causes) and 20 patients diagnosed as primary ventricular hemorrhage, 1702 patients with primary intraparenchymal hemorrhage were included. Moreover, 294 patients underwent surgical procedures (including craniotomy hematoma removal, hematoma puncture, extraventricular drainage, and so on), 15 patients with anticoagulant therapy before symptom onset, 588 patients with missing data on the non-HDLC level, and 139 patients lost to follow-up at 1-year were excluded. Eventually, 666 patients with spontaneous ICH from 13 sites were included (Figure 1).

Baseline information

Demographic information including age, sex, onset to admission time, past medical history (including hypertension, diabetes mellitus, hyperlipidemia, cerebral infarction, and ICH), personal habits (including smoking and drinking status), and medication history (including antiplatelet and statin therapy) of each patient was collected using a standard questionnaire at baseline. Neurological deficits were assessed using the National Institute of Health Stroke Scale (NIHSS)

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and Glasgow Coma Scale (GCS) score by experienced neurologists on admission. Meanwhile, systolic and diastolic blood pressure (BP) were measured. A cranial CT scan was performed on admission and hematoma volume was then calculated as ABC/2 volumetric formula at each site.^[9] The location of hematoma was further subdivided into supratentorial and infratentorial regions. ICH score was calculated based on five parameters, GCS score, ICH volume, the presence of intraventricular extension, location of hematoma, and age.^[10]

Measurement of non-HDLC levels and other biochemical parameters

Blood samples were drawn from the antecubital vein the next morning after an overnight fast and analyzed within 4h. Total cholesterol (TC) was measured using the end-point test method and high-density lipoprotein cholesterol (HDL-C) was measured using a direct method. Non-HDLC was thus calculated by subtracting HDL-C from TC. Based on the National Lipid Association Recommendations,^[11] non-HDLC levels were categorized into five groups: desirable, <3.4mmol/L; above desirable, 3.4-4.2mmol/L; borderline high, 4.2-5.0mmol/L; high, 5.0-5.8 mmol/L; and very high, \geq 5.8 mmol/L. Accordingly, we integrated the last three groups into one group (\geq 4.2mmol/L) due to the limited number of patients.

For other biochemical parameters, random blood glucose was measured via the hexokinase/glucose-6-phosphate dehydrogenase method, serum creatinine was measured through rate reflectance spectrophotometry, white blood cell (WBC) together with platelet count were performed on EDTA with an ADVIA 120 counter (Siemens Healthcare Diagnostics, Saint-Denis, France).

Follow-up information and definition of 1-year ICH prognosis

Patients were followed up at 1-year after ICH onset via telephone interviews. Follow-up evaluation was performed by neurologists who were blinded to prognostic factors. 1-year prognosis of patients was evaluated by modified Ranking Scale (mRS) score and categorized as favorable (mRS<3) and unfavorable functional outcome groups (mRS≥3). Newly diagnosed stroke and the subtypes of stroke (both ischemic stroke and intracerebral hemorrhage) during the 1-year follow-up period were also documented.

Patient and public involvement

No patients were involved.

Statistical analysis

 The patients were divided into three groups according to the clinical diagnosis of abnormal non-HDLC levels. Continuous variables were presented as median with interquartile range (IQR), categorical variables were described as count with percentage. The group differences of continuous variables were analyzed using ANOVA or Kruskal-Wallis test as appropriate, and for categorical variables, chi-squared tests were performed. Logistic regression was used to evaluate the association between non-HDLC levels and 1-year prognosis of ICH patients, with the lowest non-HDLC group (<3.4mmol/L) used as the reference. Both the univariate and multivariate analyses were conducted to estimate the odds ratios (ORs) and 95% confidence intervals (CIs). Kaplan-Meier curves were generated and the log-rank test was employed to perform comparisons between the non-HDLC levels. Cox proportional hazards regression analysis was

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used to evaluate the risk of stroke and stroke subtypes, expressed as the hazard

ratios (HRs) and 95% CIs. Multiple regression models were run as follows. Model 1 was adjusted for age and sex. Model 2 was adjusted for variates in model 1 plus premorbid mRS score (<3 or \geq 3), history of ICH, glucose on admission, WBC on admission, baseline hematoma volume, hematoma location, time from onset to initial non-contrast CT, GCS score at admission, and systolic BP. *P*-values for trend were conducted using the three categories of non-HDLC as ordinal variables in the model. Additionally, sensitivity analysis was performed in ICH patients without statin use after admission (n=589). A 2-sided value of *p*<0.05 was considered statistically significant. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

A total of 666 eligible patients were included, with a mean age of 59 years old (ranging from 51 to 68) and 69.1% (460/666) of them were males. Amongst them, 33.5% (223/666) were identified as 1-year poor outcomes, the proportion of which were 38.4%, 30.3%, and 24.2% from <3.4mmol/L group to \geq 4.2mmol/L group.

Baseline characteristics

There were significant differences in age, prior statin use, diastolic BP, glucose on admission, WBC on admission, and statin use after admission among the three categories of non-HDLC levels (p<0.05, Table 1). Those with higher lipid levels were more likely to be younger, not a prior statin user, having higher diastolic BP and glucose on admission. While no statistical significance

was observed in sex, premorbid mRS scale, onset to admission time, past medical history,

personal habits, prior antiplatelet use, NIHSS score, GCS score, SBP, creatinine, infections, time

from onset to initial NCCT, hematoma volume, hematoma location, and ICH score between the

three groups.

Table 1. Baseline characteristics of participants according to non-HDLC levels.

17	Table 1. Baseline chara	cteristics of particip	ants according to m	OII-HDLC levels.		
19		Tatal		non-HDLC levels		D l
20		Total	<3.4mmol/L	3.4-4.2mmol/L	≥4.2mmol/L	- P-value
21	n (%)	666	359 (53.9)	175 (26.3)	132 (19.8)	
22	Age, years	59 (51, 68)	61 (53, 70)	57 (49, 67)	54 (48, 64)	<0.001
23	Male, n (%)	460 (69.1)	258 (71.9)	120 (68.6)	82 (62.1)	0.116
24	Onset to admission time, h	4.0 (1.8, 11.9)	3.8 (1.7, 11.1)	4.0 (2.0, 11.0)	4.0 (1.8, 14.7)	0.840
25 26	Premorbid mRS score					0.614
26 27	mRS<3	643 (96.5)	345 (96.1)	171 (97.7)	127 (96.2)	
27	mRS≥3	23 (3.5)	14 (3.9)	4 (2.3)	5 (3.8)	
20 29	Hypertension, n (%)	479 (71.9)	256 (71.3)	124 (70.9)	99 (75.0)	0.676
30	Diabetes mellitus, n (%)	106 (15.9)	55 (15.3)	29 (16.6)	22 (16.7)	0.902
31	Hyperlipidemia, n (%)	68 (10.2)	36 (10.0)	18 (10.3)	14 (10.6)	0.982
32	History of Cl, n (%)	102 (15.3)	58 (16.2)	27 (15.4)	17 (12.9)	0.670
33	History of ICH, n (%)	20 (3.0)	15 (4.2)	3 (1.7)	2 (1.5)	0.141
34	Smoking, n (%)	223 (33.5)	127 (35.4)	57 (32.6)	39 (29.6)	0.458
35	Drinking, n (%)	256 (38.4)	139 (38.7)	69 (39.4)	48 (36.4)	0.850
36	Prior antiplatelet use, n (%)	110 (16.5)	61 (17.0)	28 (16.0)	21 (15.9)	0.771
37	Prior statin use, n (%)	44 (6.6)	31 (8.6)	10 (5.7)	3 (2.3)	0.036
38	NIHSS score on admission	8 (3, 13)	9 (3, 15)	7 (3, 13)	5 (2, 12)	0.083
39	GCS score on admission	14 (12, 15)	14 (12, 15)	15 (13, 15)	15 (13, 15)	0.063
40	SBP on admission, mmHg	160 (149, 183)	160 (150, 180)	160 (145, 183)	162 (150, 183)	0.564
41 42	DBP on admission, mmHg	95 (83, 105)	92 (80, 102)	96 (85, 106)	97 (85, 109)	0.024
42 43	Glucose on admission, mmol/L	6.9 (5.9, 8.4)	6.6 (5.8, 8.1)	7.0 (5.9, 8.6)	7.1 (6.0, 9.3)	0.032
44	WBC on admission, 10 ⁹ /L	8.4 (6.6, 10.9)	8.1 (6.3 <i>,</i> 10.7)	9.1 (7.0, 11.7)	7.1 (6.0, 9.3)	0.007
45	Platelets on admission, 10 ⁹ /L	212 (175, 252)	202 (164, 238)	218 (180, 259)	230 (192, 265)	<0.001
46	Creatinine on admission, µmol/L	64.0 (53.0, 77.3)	64.6 (54.0 <i>,</i> 76.4)	65.0 (52.3, 79.0)	62.0 (50.1 <i>,</i> 76.0)	0.223
47	Statin use after admission, n (%)	77 (11.6)	19 (5.3)	30 (17.1)	28 (21.2)	<0.001
48	Infections, n (%)	136 (20.4)	77 (21.5)	39 (22.3)	20 (15.2)	0.239
49	Time from onset to initial NCCT, h	5.2 (2.3, 16.7)	5.2 (2.2 <i>,</i> 14.8)	5.1 (2.3, 19.6)	4.8 (2.3 <i>,</i> 19.4)	0.738
50	Baseline hematoma volume, ml	10.5 (5.0, 23.4)	10.7 (5.0, 25.0)	10.4 (5.5, 23.1)	10.0 (4.9 <i>,</i> 16.8)	0.379
51	Hematoma location					0.251
52	Supratentorial, n (%)	599 (89.7)	327 (91.2)	155 (88.2)	117 (87.5)	
53	Infratentorial, n (%)	67 (10.3)	31 (8.8)	23 (11.8)	16 (12.5)	
54	Secondary ventricular hemorrhage	181 (27.2)	100 (27.9)	43 (24.6)	38 (28.8)	0.652
55	ICH score	0 (0, 1)	0 (0, 1)	0 (0, 1)	0 (0, 1)	0.447
56 57	Values are (%) for cates	gorical variables and	l median (IQR) for c	ontinuous variables.		
57	mRS, modified Rankin	-				

mRS, modified Rankin Scale; CI, cerebral infarction; ICH, intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale; SBP, systolic blood

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pressure; DBP, diastolic blood pressure; WBC, white blood cells; NCCT, non-contrast CT.

Correlation between baseline non-HDLC and 1-year prognosis in ICH patients

In the univariate analysis, higher non-HDLC levels were significantly associated with decreased risk of 1-year poor outcome (p=0.002). Patients who achieved non-HDLC above 4.2mmol/L had a 49% lower risk of poor functional outcome at 1 year (OR 0.51, 95% CI 0.33-0.81). While no statistical difference was retained after adjusting for age, sex, and potential confounding factors (p>0.05). In the fully adjusted model (Model 2), the OR values were 1.00 (reference), 1.06 (0.63, 1.79), and 0.83 (0.45, 1.54) from the lowest to the highest non-HDLC group. Moreover, the results maintained consistency in sensitivity analysis among patients without statin use after admission (p=0.842, Table 2).

Table 2. Odds ratios and 95% CI for 1-year poor outcome (mRS \geq 3) according to non-HDLC levels.

		non-HDLC levels		Continuous conto	
-	<3.4mmol/L	3.4-4.2mmol/L	∠≥4.2mmol/L	Continuous scale	P for trenc
1-year poor outcome, n (%)	138 (38.4)	53 (30.3)	32 (24.2)		
Univariate analysis	Ref.	0.70 (0.47, 1.02)	0.51 (0.33, 0.81)	0.71 (0.58, 0.88)	0.002
Multivariate analysis					
Model 1	Ref.	0.82 (0.54, 1.23)	0.66 (0.41, 1.06)	0.81 (0.65, 1.02)	0.075
Model 2	Ref.	1.06 (0.63, 1.79)	0.83 (0.45, 1.54)	0.89 (0.76, 1.05)	0.694
Sensitivity analysis	Ref.	0.92 (0.53, 1.61)	1.12 (0.58, 2.16)	0.92 (0.78, 1.08)	0.842

Data are OR (95% CI) unless otherwise stated. Model 1 adjusted for age and sex. Model 2 adjusted for variates in model 1 plus premorbid mRS score (<3 or ≥3), history of ICH, glucose on admission, WBC on admission, baseline hematoma volume, hematoma location, time from onset to initial non-contrast CT, GCS score at admission, systolic blood pressure.

Sensitivity analysis was performed in ICH patients without statin use after admission (n=589), and adjusted for variates in model 2.

Notably, age, premorbid mRS score (<3 or ≥3), and baseline hematoma volume were positively

associated with 1-year poor prognosis in the multivariate analysis. Whereas, higher GCS score at

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admission was an independent predictor of favorable outcomes. Additional detailed information was given in Figure 2.

In the process of statistics, we also calculated the association between the quartiles of non-HDLC with 1-year poor outcome (data was shown in Supplementary Table 1). The highest quartile of non-HDLC was significantly associated with decreased risk of 1-year poor outcome, while no statistical difference was retained after adjusting for confounding factors. Due to the identical results of the two cut-off methods, we thus chose the risk-stratified levels of non-HDLC which had more instructive clinical significance.

Correlation between baseline non-HDLC and stroke risk

We further investigated the correlation between non-HDLC levels and another stroke (ischemic or hemorrhagic) risk. In univariate analysis, the cumulative incidences of total stroke, ischemic stroke, and ICH were not statistically different among non-HDLC levels (log-rank test, all P > 0.05, Figure 3). In multivariate analysis, no correlation was identified between the three groups either (Table 3). When the quartile of non-HDLC was set as the cut-off, similar negative results were also obtained (data was not shown).

Table 3. Hazard ratios for stroke according to non-HDLC levels.

2 3			non-HDLC levels			Per 1 SD increase
54		<3.4mmol/L	3.4-4.2mmol/L	≥4.2mmol/L	- P for trend	Per I SD IIICrease
55	Total stroke					
56	Events, n (%)	10 (2.8)	6 (3.4)	3 (2.3)		
57	Model 1	Ref.	1.06 (0.38, 2.94)	0.71 (0.19, 2.61)	0.88 (0.49, 1.59)	0.96 (0.67 <i>,</i> 1.39)
58	Model 2	Ref.	1.44 (0.50, 4.22)	0.83 (0.21, 3.25)	0.98 (0.54, 1.80)	1.00 (0.74, 1.35)
59	Ischemic stroke					
50	Events, n (%)	6 (1.7)	2 (1.1)	2 (1.5)		
			11			

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1 2							
2	Model 1		Ref.	0.56 (0.11, 2.79)	0.75 (0.15, 3.79)	0.81 (0.35, 1.86)	0.94 (0.61, 1.47)
4	Model 2		Ref.	0.73 (0.14, 3.89)	0.65 (0.12, 3.67)	0.80 (0.34, 1.86)	0.99 (0.75, 1.32)
5		al hemorrhage			,,	,,	
6 7	Events, n (%	5)	4 (1.1)	4 (2.3)	2 (1.5)		
8	Model 1		Ref.	1.86 (0.46, 7.52)	1.24 (0.22, 6.89)	1.18 (0.55, 2.54)	1.01 (0.53, 1.94)
9	Model 2		Ref.	2.84 (0.61, 13.14)	1.80 (0.28, 11.53)	1.41 (0.63, 3.19)	1.07 (0.52, 2.21)
10		Data are HR (95	5% CI) unless ot	herwise stated.			
11		Model 1 adjust	ed for age and	sex.			
12 13		Model 2 adjust	ed for variates	in model 1 plus pric	or mRS scale (<3 or ≥	3) history of ICH, gl	ucose
14		on admission,	WBC on admis	sion, baseline hemat	oma volume, hema	toma location, time	from
15		onset to initial	non-contrast C	T, GCS score at admis	sion, systolic blood p	ressure.	
16							
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20		DISCUSSION					
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22		This study pro	ovided evidenc	e on the associatio	n between non-HD	LC levels and long	g-term
23 24							
25		functional outo	omes in ICH p	atients. Although no	on-HDLC was a signi	ficant 1-year predic	tor in
26							
27		univariate anal	ysis, it did not	retain its independ	ent prognostic value	in multivariate an	alysis.
28 29					1 0		,
29 30		Moreover stati	in use after ICH	onset made no diffe	rence to the long-ter	m prognosis	
31						in prognosisi	
32		In our study	the provalence	e of 1-year function	al independence in	ICH nationts was	66 5%
33		in our study,		e of 1-year function	al independence in	ien patients was	00.576
34 35		(442/CCC) for					
36		(443/000), Tar	outweigning	the data previously	reported. ¹⁴ Accordi	ng to the inclusion	n anu
37			_		4	A	
38		exclusion criter	ia, severe case	s who underwent su	rgical treatment or le	ost to follow-up we	re not
39 40							
40 41		enrolled. It is no	oteworthy that	per 1 mmol/L increm	ent in non-HDLC yie	lded a 29% decrease	ed risk
42							
43		of 1-year poor	prognosis (cru	de OR 0.71, 95% CI ().58-0.88). However,	contrary to our pre	evious
44							
45 46		research findin	g of the indepe	endent role of non-H	DLC on short-term fu	inctional outcomes,	^[7] the
47							
48		results of this	study showed	d that age, premort	oid mRS score, base	eline hematoma vo	lume,
49			·				
50 51		admission GCS	score. rather	than non-HDLC level	. were independent	predictors for long	-term
52					,	p	,
53		functional out	comes in ICH	patients. The valida	ated predictors mer	tioned above kent	high
54				patients. The value			
55 56		conformity	a tha itama in l	CH Eurotional Outaa	no Scoro an offactio	o prognostic model	for 1
56 57		comormity with	i die items in l	CH Functional Outco	ne score, an effectiv	e prognostic model	101 1-
58		-		6 [12] ·			
59		year poor func	tional outcome	es after ICH, ^[12] where	as the absolute mag	nitude effect of low	/ non-
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HDLC level on ICH prognosis was likely to be small and overshadowed with time. Beyond that, the amount of rehabilitation with functional gains might also be related.^[13]

It was reported that low levels of LDL-C and TC were associated with hematoma expansion.^[14, 15] As containing all the atherogenic lipoproteins, non-HDLC was served as the preferred target of lipid-lowering therapy.^[16] The potential mechanisms regarding the association between hypolipidemia and hematoma expansion, including impaired endothelial integrity,^[17] necrotic medial smooth muscle cells,^[18] increased erythrocyte fragility,^[19] inhibited platelet aggregation,^[20] and the resultant incident cerebral microbleeds.^[21] Despite the theoretical basis, our study failed to show an independent correlation between non-HDLC levels and 1-year functional outcomes in ICH patients. The secondary injury caused by low levels of lipoproteins in ICH patients was associated with short-term prognosis (30-day, 3-month),^[22, 23] while its impact on long-term prognosis (1-year) was negative, which merits further investigation due to the limited sample size and incomplete neuroimaging data on hematoma expansion in our study. Statin treatment is another major concern,^[24] there were respectively 6.6% (44/666) and 11.6% (77/666) patients with pre- and post-stroke statin use in our study. Two recent meta-analyses concluded that there was no evidence to suggest pre-stroke statin therapy may increase bleeding risk in the context of ICH.^[25, 26] Whether to start, continue, or stop statin treatment in ICH patients has aroused great concern, we thus conducted a sensitivity analysis to evaluate the effect of statin exposure after admission on ICH prognosis. No significant difference was detected between non-HDLC levels and 1-year prognosis in ICH patients in our study, irrespective of post-stroke statin use. A recent review indicated that statin should be applied after weighing the pros and cons given its pleiotropic as well as lipid-lowering effects.^[27] Because of the

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relatively low stain exposure rate in our study, it is necessary to conduct randomized controlled trials around this topic.

Our study filled the vacancy about the association between non-HDLC and 1-year functional outcomes, simultaneously shed light on the diverse impacts of non-HDLC on short-term and long-term prognosis in ICH patients. Nonetheless, there are still some limitations. First, the follow-up radiological information was unavailable, which makes it difficult to verify the intermediate role of hematoma expansion between non-HDLC and poor prognosis. Secondly, ICH caused by cerebral amyloid angiopathy has a higher rebleeding risk than hypertensive one,^[28] while data regarding the cause of ICH was not documented in our study. Despite no correlation was observed between the history of ICH and 1-year functional outcome, the impact of ICH etiology merits further investigation. Thirdly, medication therapy regarding antiplatelet or anticoagulation agents were not included in the multivariate analysis, whereas accumulating researches proved that antithrombotic treatment increased the risk of cerebral microbleeds as well as future ICH.^[29, 30] Although we collected pre-ictus antiplatelet use, restricted by the small sample size, further research is needed to provide insight into the relationship. Moreover, since our study based on a highly selected population with small hematoma and relatively good neurologic status to achieve precise research, the findings cannot be generalized to the whole ICH population.

CONCLUSION

In conclusion, non-HDLC was not an independent predictor for 1-year functional outcome in ICH patients, irrespective of post-stroke statin use. The predictive value of well-recognized

confounding factors was more dominant than non-HDLC on long-term poor prognosis. Further prospective studies are needed to assess the impact of lower non-HLDC levels on ICH prognosis.

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Contributors YW and JW performed the experiments, interpreted the results of statistical analysis, and drafted the manuscript. AW conducted the statistical analysis and interpreted the data. RJ revised the manuscript for intellectual content. WW and XZ had full access to all of the data and take responsibility for the integrity of the data and the accuracy of the data analysis.

Funding Our study was supported by grants from the Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences (2019-I2M-5-029), Beijing Natural Science Foundation (Z200016), Beijing Municipal Committee of Science and Technology (Z201100005620010), and Ministry of Science and Technology of the People's Republic of China (2018YFC1705003).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The study was approved by the Central Institutional Review Board of Beijing

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Tiantan Hospital (KY2014-023-02) and written informed consent was obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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Figure Legends

Figure 1. Flow chart for selection of study participants.

ICH, intracerebral hemorrhage; non-HDLC, non-high-density lipoprotein cholesterol.

Figure 2. Multivariate predictors of 1-year poor outcome among ICH patients.

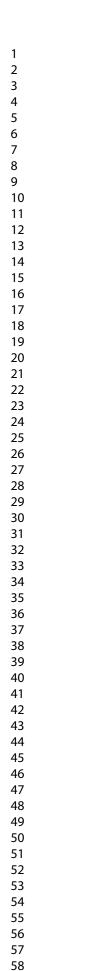
Non-HDLC, non-high-density lipoprotein cholesterol; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; WBC, white blood cells; NCCT, non-contrast CT; GCS, Glasgow Coma Scale; SBP, systolic blood pressure.

Figure 3. Cumulative incidences of (A) total stroke, (B) ischemic stroke, and (C) intracerebral hemorrhage according to non-HDLC levels.

Non-HDLC, non-high-density lipoprotein cholesterol.

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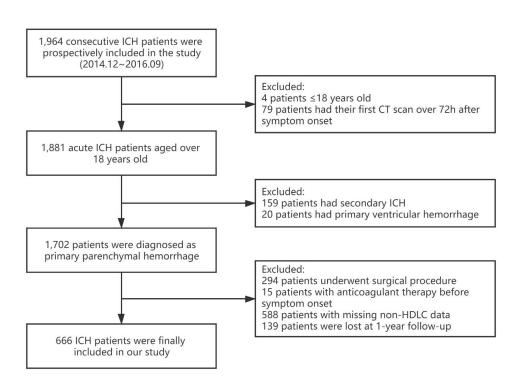


Figure 1. Flow chart for selection of study participants. ICH, intracerebral hemorrhage; non-HDLC, non-high-density lipoprotein cholesterol.

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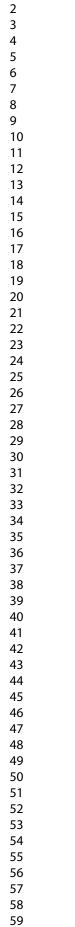
Variables	Poor outcome (mRS ≥3, n=178)	Odds ratio (95% CI)
non-HDLC (vs <3.4mmol/L)		
3.4-4.2mmol/L	1.06 (0.63, 1.79)	⊢⊢ -1
≥4.2mmol/L	0.83 (0.45, 1.54)	⊢ ♦1
Age, years	1.08 (1.06, 1.10)	•
Male	0.84 (0.52, 1.36)	⊢ ♦−1
Premorbid mRS score ≥3	3.89 (1.43, 6.77)	↓ → → → → → → →
History of ICH	2.80 (0.95, 5.27)	↓ i
Glucose on admission, mmol/L	1.02 (0.95, 1.11)	
WBC on admission, 10E9/L	1.00 (0.93, 1.08)	*
Platelet on admission, 10E9/L	1.00 (0.99, 1.00)	+
Baseline hematoma volume, mL	1.02 (1.01, 1.04)	•
Infratentorial hemorrhage	0.82 (0.37, 1.82)	⊢ • − −1
Tme from onset to initial NCCT, hours	0.99 (0.98, 1.01)	+
GCS score on admission	0.73 (0.66, 0.80)	*
SBP, mmHg	0.99 (0.99, 1.00)	+
		1.0 2.0 4.0 6.0

Figure 2. Multivariate predictors of 1-year poor outcome among ICH patients.

Non-HDLC, non-high-density lipoprotein cholesterol; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; WBC, white blood cells; NCCT, non-contrast CT; GCS, Glasgow Coma Scale; SBP, systolic blood pressure.

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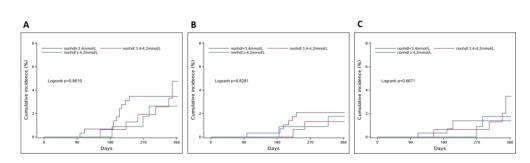


Figure 3. Cumulative incidences of (A) total stroke, (B) ischemic stroke, and (C) intracerebral hemorrhage according to non-HDLC levels.

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	non-HDLC (quartiles.					
			non-H	DLC quartiles		- Continuous scale	P for tren
		Q1	Q2	Q3	Q4		PIOLITEIN
L-year poor outco	me, n (%)	71 (43.3)	58 (34.5)	54 (32.3)	40 (24.0)		
Onivariate analysi		Ref.	0.69 (0.44, 1.08)	0.63 (0.40, 0.98)	0.41 (0.26, 0.66)	0.76 (0.66, 0.88)	<0.001
1 Multivariate analy 2	sis						
Model 1		Ref.	0.80 (0.50, 1.29)	0.84 (0.52, 1.36)	0.57 (0.35, 0.95)	0.85 (0.73, 1.00)	0.049
1 Model 2		Ref.	0.81 (0.44, 1.50)	1.03 (0.56, 1.90)	0.71 (0.37, 1.37)	0.93 (0.76, 1.14)	0.468
Sensitivity analysi	5	Ref.	0.83 (0.43, 1.60)	1.14 (0.60, 2.18)	0.76 (0.39, 1.51)	0.96 (0.77, 1.18)	0.673
7	Data are Ol	R (95% Cl) un	less otherwise state	d.			
3	Model 1 ad	ljusted for ag	e and sex.				
9	Model 2 ad	ljusted for va	riates in model 1 plu	us prior mRS scale (<	<3 or ≥3) history of I	CH, glucose on	
) 1	admission,	WBC on adm	nission, baseline her	natoma volume, he	matoma location, ti	me from onset	
<u>)</u>	to initial no	on-contrast C	T, GCS score at admi	ssion, systolic blood	l pressure.		
3	Sensitivity	analysis was j	performed in ICH pa	tients without stati	n use after admissio	n (n=589), and	
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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(<i>a</i>) Indicate the study's design with a commonly used term in the title or the abstract	1
		(<i>b</i>) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(<i>a</i>) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5,7
		(<i>b</i>) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(<i>a</i>) Describe all statistical methods, including those used to control for confounding	7
		(b) Describe any methods used to examine subgroups and interactions	7
		(c) Explain how missing data were addressed	NA
		(d) If applicable, explain how loss to follow-up was addressed	NA
		(<i><u>e</u></i>) Describe any sensitivity analyses	7
Doculto			
Results Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study,	5
		completing follow-up, and analysed (b) Give reasons for non-perticipation at each stage	5
		(b) Give reasons for non-participation at each stage(c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social)	8
		and information on exposures and potential confounders	5
		(b) Indicate number of participants with missing data for each variable of interest(c) Summarise follow-up time (eg, average and total amount)	NA
		(c) summarise tonow-up time (eg. average and total amount)	1 1 1 1

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Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their	9
		precision (eg, 95% confidence interval). Make clear which confounders were adjusted for	
		and why they were included	
		(b) Report category boundaries when continuous variables were categorized	9-
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a	N
		meaningful time period	
Other analyses	17	Report other analyses done-eg analyses of subgroups and interactions, and sensitivity	9
		analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision.	12
		Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations,	10
		multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other informati	on		
Funding	22	Give the source of funding and the role of the funders for the present study and, if	13
		applicable, for the original study on which the present article is based	

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.