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ORIGINAL ARTICLE

Exploring metabolic and inflammatory abnormalities in rheumatoid arthritis patients developing stroke disease: a case-control study using electronic medical record data in northern China

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Abstract

Objectives Intend to investigate the roles of serum lipids, inflammatory markers, and serological status in rheumatoid arthritis and stroke patients by using case-control study.

Materials and methods Clinical data were retrieved from the electronic medical record of the First Affiliated Hospital of China Medical University during January 2011 to March 2018. The obtained data were categorized into case groups and three control groups, in the ratios of 1:2, respectively, with all matching age and gender. Multinomial logistic regression analysis and restricted cubic spline were conducted examining the associations between serum lipids, inflammatory markers, serological status, and the risk of stroke among RA patients.

Results The present studies included 1057 study subjects. The elevated ESR, LDL-C levels, and much higher CRP levels ≥ 230 mg/L were independent risk factors for RA patients in developing stroke. Furthermore, we found that ESR and LDL-C levels could exhibit a linear association with the risk of comorbid stroke while CRP level had a nonlinearity association with stroke risk among RA patients.

Conclusions A close monitoring is required for RA patients with dyslipidemia and elevated inflammatory markers, and the primary stroke preventive strategies should be directed against these risk factors.

Keywords Dyslipidemia · Inflammatory marker · Rheumatoid arthritis · Serum lipids · Stroke

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disease characterized by erosion and symmetric polyarthritis [1] and a globally distributed disease, and is one of the leading causes of work disability, with morbidity rates of 0.32~0.36% in China and the highest is 0.5% in northeast China [2]. Previous studies have reported that RA patients are susceptible to serious complications, including atherosclerosis, myocardial infarction, and stroke [3, 4], which can be influenced by age, sex, traditional risk factors of CVD, degree of joint pain, and inflammation [5]. RA has been identified as a risk factor of stroke [6, 7], but the correlation between serum biochemical parameters and RA patients with stroke remains controversial. It is proposed that the risk of stroke among RA patients may be closely related to the elevated levels of erythrocyte sedimentation rate (ESR), high-density lipoprotein cholesterol (HDL_C) [8], total cholesterol (TC), triglyceride (TG) [9, 10], anticyclic citrullinated peptide antibody (anti-CCP) [5], interleukin-6, low-density lipoprotein cholesterol (LDL_C), and C-reactive protein (CRP) [8, 11–13]. Overall, the role of serum lipids, inflammatory markers, and serological status, and the prevalence of stroke in RA patients remain unclear, especially in regard to serum lipid level.

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Thus, we conduct this study using real-world data to investigate the risk of stroke in RA patients by comparing the serum biochemical markers among RA patients (with and without stroke), stroke patients, and control subjects.

Patients and methods

Study subjects

Data of all aged 18 and older patients diagnosed of RA and stroke were searched from electronic medical record (EMR) of a third-senior hospital in Liaoning province, by using *the International Classification of Diseases Tenth Revision* (ICD-10) of the Beijing clinical version (RA: M05.x~06.x. stroke: I60 I60.1-I60.0 I61 I61.0-I61.9 I69.0 I69.1 I63 I63.0-I63.9 I69.3. appendicitis: K35.x~37.x) during January 2011 to March 2018. The obtained data were then classified according to (i) RA patients with stroke (named as RA+stroke group); (ii) age- and sex-matched RA patients without stroke (named as RA group); (iii) stroke patients without RA (named as stroke group); and (iv) age- and sex-matched health control group (appendicitis patients without stroke and RA, to simulate the serum biochemical level of the general health population), with 1:2 ratios of RA+stroke group: three control groups respectively. The inclusion criteria of screening research objects were as follows: (i) RA patients were diagnosed based on the RA diagnostic classification criteria [14] revised by American College of Rheumatology (ACR) and the new RA diagnostic criteria introduced by ACR and European League Against Rheumatism (EULAR); (ii) stroke patients were diagnosed according to the CVD criteria adopted at the Fourth Academic Conference by *the Chinese Neuroscience Society* in 1995 [15]; (iii) all patients received one or more laboratory assessment (i.e., serum inflammatory, antibody, complement, lipid assays). Meanwhile, patients were excluded if they met the following criteria: (i) RA patients diagnosed with coronary heart disease (CHD) based on the American Heart Association (AHA) guidelines for coronary angiography (CAG); (ii) patients who suffered from connective tissue diseases, including systemic lupus erythematosus, scleroderma, dry syndrome, and sclerodermatitis; (iii) RA patients with coexisting ankylosing spondylitis and gout arthritis. The same inclusion and exclusion criteria were applied to the three control groups. In addition, inpatients were informed that their EMRs might be used in scientific research in the future upon their admission and signed inform consent form.

Data collection and definition

The following data were obtained from EMR: (i) demographic and clinical characteristics, including age, gender, menstruation of female including age at menses and age at menopause, body mass index (BMI), cigarette-smoking history, alcohol-drinking history, and comorbidities; (ii) lipid profiles such as sera TC, TG, LDL-C, and HDL-C. (iii) serologic profiles of RA patients, including CRP, ESR, rheumatoid factor (RF), complement 3 (C3), complement 4 (C4), and anticyclic citrullinated peptide (anti-CCP) antibodies; (iv) medications use: traditional disease-modifying anti-rheumatic drugs (DMARDs), biologic DMARDs. Comorbidities merely including hypertension and diabetes in our study are defined according to the diagnoses of clinical doctors from EMR. Laboratory tests were carried out using overnight fasting venous blood samples and conducted as clinical standard operating procedures for inspection items (SOP).

Elevated levels of serological profiles were defined as CRP ≥ 8 mg/l, ESR ≥ 20 mmH_2O, RF ≥ 20 IU/ml, and CCP ≥ 50 U/ml; abnormal levels were C3 < 0.79 or ≥ 1.52 g/l, C4 < 0.16, or ≥ 0.38 g/l; and fasting blood glucose (FBG) < 3.9 or ≥ 6.1 mmol/L, according to clinic laboratory inspection reference ranges in China. Moreover, the Chinese Adult Dyslipidemia Prevention Guide (2012 and 2016 revised edition) diagnostic criteria [16, 17] were referred to delineate the abnormal cutoff points of dyslipidemia, shown in Table 1. In addition, the results of multiple laboratory tests at different time points were assessed during the initial data filtering, and selecting the first laboratory test results among inpatients, while we select the first laboratory test results of first admission due to stroke among RA+stroke patients.

Statistical analysis

Clinical characteristic description and univariate analysis

The results of demographic, clinical, and laboratory parameters were expressed as mean ± standard deviation (SD) for quantitative data and percentages for categorical data by group. After conducting the normality test, quantitative data of all case and control groups were compared by Kruskal–Wallis one-way analysis of variance (ANOVA). Subsequently, post hoc Dunn's multiple comparison test was carried out to compare the differences between RA+stroke group and other control groups; meanwhile, the categorical data was analyzed with chi-squared test; above two tests are with two-tailed by using Graph Pad Prism 6.0 software.

Potential confounder adjustment and multivariate analysis

Multiple control groups, propensity score matching (PSM), and multivariate logistic regression analysis were performed to adjust potential confounders and further to explore the association between lipid levels, inflammatory markers, and risk of stroke among RA patients. PSM was performed in the context of case: three control ratios of 1:2 matching to balance the effects of age and sex among four groups, by using optimal

Table 1 Cutoff points of dyslipidemia among participants (mmol/L)

Categorical data	TC	LDL-c	HDL-c	TG
Normal level	< 5.20	< 3.40	≥ 1.55	< 1.70
Edge higher level	≥ 5.20 and < 6.20	≥ 3.40 and < 4.10	–	≥ 1.70 and < 2.30
High level	≥ 6.20	≥ 4.10	–	≥ 2.30
Edge lower level	–	–	≥ 1.04 and < 1.55	–
Low level	–	–	< 1.04	–

TC total cholesterol, *LDL_c* low-density lipoprotein cholesterol, *HDL_c* high-density lipoprotein cholesterol, *TG* triglycerides

method of MatchIt package in R software version 3.4.4. For the analysis of serum biochemical marker levels, binary logistic regression was used to filter the risk factors of RA+stroke group compared to other groups separately, meanwhile comparing these final models to adjust confounders, in which the probability for stepwise entry was 0.05 and the probability of stepwise removal was 0.1, by using SPSS software version 23.0.

Dose-response analysis

Restricted cubic spline was adopted to estimate the potential linear or nonlinear association between biochemical marker levels and the risk of stroke among RA patients in SAS software version 9.3. The 0.05 was considered statistically significant.

Results

Baseline demographics and clinical characteristics

A total of 8585 RA patients meet the prerequisite for RA diagnostic classification criteria with 6.71% prevalence of stroke (576 RA+stroke patients) during January 2011 to March 2018. Finally, 151 RA+stroke patients, 302 RA patients, and 302 stroke patients, 302 control subjects meet the inclusion and exclusion criteria to entry into this retrospective case-control study (Fig. 1). As shown in Table 2, the mean age and male:female ratio of RA+stroke group were 69.61 ± 12.83 years and 1:3.31, respectively, which were not significantly different as compared to three control groups ($P > 0.05$). For the female in RA+stroke group, the mean age of menarche and menopause was 19.91 ± 4.66 and 50.27 ± 3.37 years, respectively, and the differences were not significant among the four groups.

Univariate analysis among four groups indicated that the distribution of comorbid hypertension in RA+stroke group was significantly higher than that in the health control group (56.95% vs. 15.56%, $P < 0.05$), but significantly lower than that in the RA group (56.95% vs. 73.77%, $P < 0.05$). Similarly, the frequencies of comorbid hypertension in the RA group (73.77% vs. 15.56%, $P < 0.05$) and stroke group (60.71% vs. 15.56%, $P < 0.05$) were significantly increased as compared to the health control group. The proportion of comorbid diabetes in the RA+stroke group was significantly lower than that in the RA group (18.54% vs. 23.5%, $P < 0.05$) and stroke group (18.54% vs. 32.65%, $P < 0.05$), but higher than that in the health control group (18.54% vs. 5.96%, $P < 0.05$); the frequencies of comorbid diabetes in the stroke group were significantly increased as compared to the health control group (32.65% vs. 5.96%, $P < 0.05$). The distribution of smokers was significantly different between the RA+stroke group and health control group as well as between the RA+stroke group and stroke group. Meanwhile, the distributions of alcohol consumption were significantly different in the RA+stroke and stroke groups, when

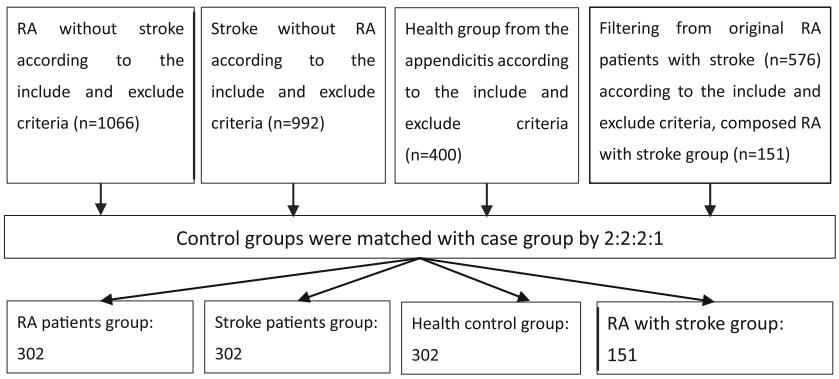

Fig. 1 Flow chart showing the selection process of study participants. RA, rheumatoid arthritis; EMR, the electronic medical record; PSM, propensity score matching

Table 2 Patient baseline demographics and clinical characteristics among RA patients with stroke, RA patients, stroke patients, and normal participants

Variables	Normal ($n = 302$)	Stroke ($n = 302$)	RA ($n = 302$)	RA+stroke ($n = 151$)
Demographics and health behaviors				
Age, mean ± SD (years)	63.44 ± 9.18	68.81 ± 10.29	69.07 ± 12.11	69.61 ± 12.83
Women, *n* (%)	206 (68.21)	233 (77.15)	232 (76.82)	116 (76.82)
Menstruation, mean ± SD (days)				
Menarche	18.25 ± 4.36	18.27 ± 4.92	20.23 ± 4.51	19.91 ± 4.66
Menopause	50.26 ± 2.59	50.45 ± 2.77	50.10 ± 2.79	50.27 ± 3.37
BMI, mean ± SD, kg/m^2	22.05 ± 2.32*#†	24.03 ± 3.38†	23.03 ± 4.57#†	23.85 ± 4.68*
Smoking, *n* (%)				
Never	254 (84.11)	2 (0.71)	15 (6.73)	5 (3.31)
Current	48 (15.89)*#†	280 (99.29)*#†	196 (87.89)#	144 (95.36)*
Past	0 (0)	0 (0)	12 (5.38)	2 (1.32)
Drinking, *n* (%)				
Never	NA	237 (84.04)	207 (89.22)	132 (87.42)
Current	NA	45 (15.96)*#	20 (8.62)*#	19 (12.58)*
Past	NA	0 (0.00)	5 (2.16)*	0 (0.00)*
Comorbidity, *n* (%)				
Hypertension	47 (15.56)*#†	119 (60.71)#†	135 (73.77)*#	86 (56.95)*
Diabetes	18 (5.96)*#†	64 (32.65)*#†	43 (23.5)*#	28 (18.54)*
Lipid profile, mean ± SD (mmol/L)				
LDL	2.36 ± 1.01*#†	3.00 ± 1.05#†	2.63 ± 0.83*#†	3.10 ± 1.42*
TC	4.15 ± 1.01*	4.82 ± 1.29*#†	4.33 ± 1.03#†	4.52 ± 1.14*†
TG	1.54 ± 1.20*	1.59 ± 1.23*#†	1.24 ± 0.71#†	1.26 ± 0.70*†
HDL	1.67 ± 1.38*#	1.22 ± 0.37#†	1.07 ± 0.33#†	1.16 ± 0.45*
Serologic profile				
RF-positive, *n* (%)	NA	14 (6.86)*#	171 (66.28)*#	121 (80.13)*
CRP,mean ± SD (mg/L)	NA	20.58 ± 44.39*#	42.84 ± 53.4*#	31.22 ± 56.75*#
FBG, mean ± SD (mmol/L)	NA	1.23 ± 0.38*#	5.51 ± 1.40*#	5.49 ± 1.67*
Anti-CCP-positive, *n* (%)	NA	NA	144 (58.78)	60 (51.72)
ESR, mean ± SD (mm/h)	NA	NA	45.95 ± 40.26*	54.23 ± 37.73*
C3, mean ± SD (g/L)	NA	NA	1.13 ± 0.33	1.00 ± 0.28
C4, mean ± SD (g/L)	NA	NA/	0.23 ± 0.08	0.21 ± 0.08
Medications use *n* (%)				
Biologic DMARDs	NA	NA	29 (9.60)	12 (7.95)
Traditional DMARDs	NA	NA	231 (76.49)	117 (77.48)

SD standard deviation, *BMI* body mass index, *LDL_c* low-density lipoprotein cholesterol, *TC* total cholesterol, *TG* triglycerides, *HDL_c* high-denspoprotein cholesterol, *RF* rheumatoid arthritis factor, *CRP* C-reactive protein, *FBG* fasting blood glucose, *Anti-CCP* anticyclic peptide containing citrulline, *ESR* erythrocyte sedimentation rate, *C3* complement 3, *C4* complement 4. *Statistically significant associations ($P < 0.05$) between RA+stroke and other three groups. # Statistically significant associations ($P < 0.05$) between RA and other three groups. † Statistically significant associations ($P < 0.05$) between stroke and other three groups. *DMARDs* disease-modifying anti-rheumatic drugs, *NA* not available

compared to the respective control groups. The use rate of traditional DMARDs among RA with stroke patients was a little higher than that among RA patients (77.48% vs.76.49%), the opposite result for biologic DMARDs (7.95% vs. 9.60%); however, these differences were not significant (shown in Table 2).

Comparison of lipid profiles and metabolic changes among the four groups

The differences in lipid profile parameters were compared among four groups. The results indicated that the serum LDL-C level in the RA+stroke group was significantly

increased as compared to the RA group ($P < 0.05$) and health control group ($P < 0.0001$), but no significant difference was found when compared to the stroke group. Likewise, the serum LDL-C level in the RA group was significantly higher ($P < 0.0001$) than that in the health control group (Fig. 2a). As illustrated in Fig. 2b, the serum TC level in the RA+stroke group was significantly higher than that in the health control group ($P < 0.001$), but significantly lower than that in the stroke group ($P < 0.05$). Furthermore, the serum TG level in the RA+stroke group was significantly higher ($P < 0.05$) than that in the health control group, while significantly lower ($P < 0.001$) than that in the stroke group (Fig. 2c). Nonetheless, serum HDL_C levels were significantly reduced in both the RA+stroke ($P < 0.05$) and RA groups ($P < 0.0001$) as compared to the health control group; serum HDL_C levels were also significantly reduced in the RA group ($P < 0.0001$) as compared to the stroke group (Fig. 2d).

In addition, as seen in Fig. 2j, the BMIs of the RA+stroke and RA groups were significantly higher as compared to the health control group ($P < 0.0001$, $P <$ 0.05, respectively), and that in

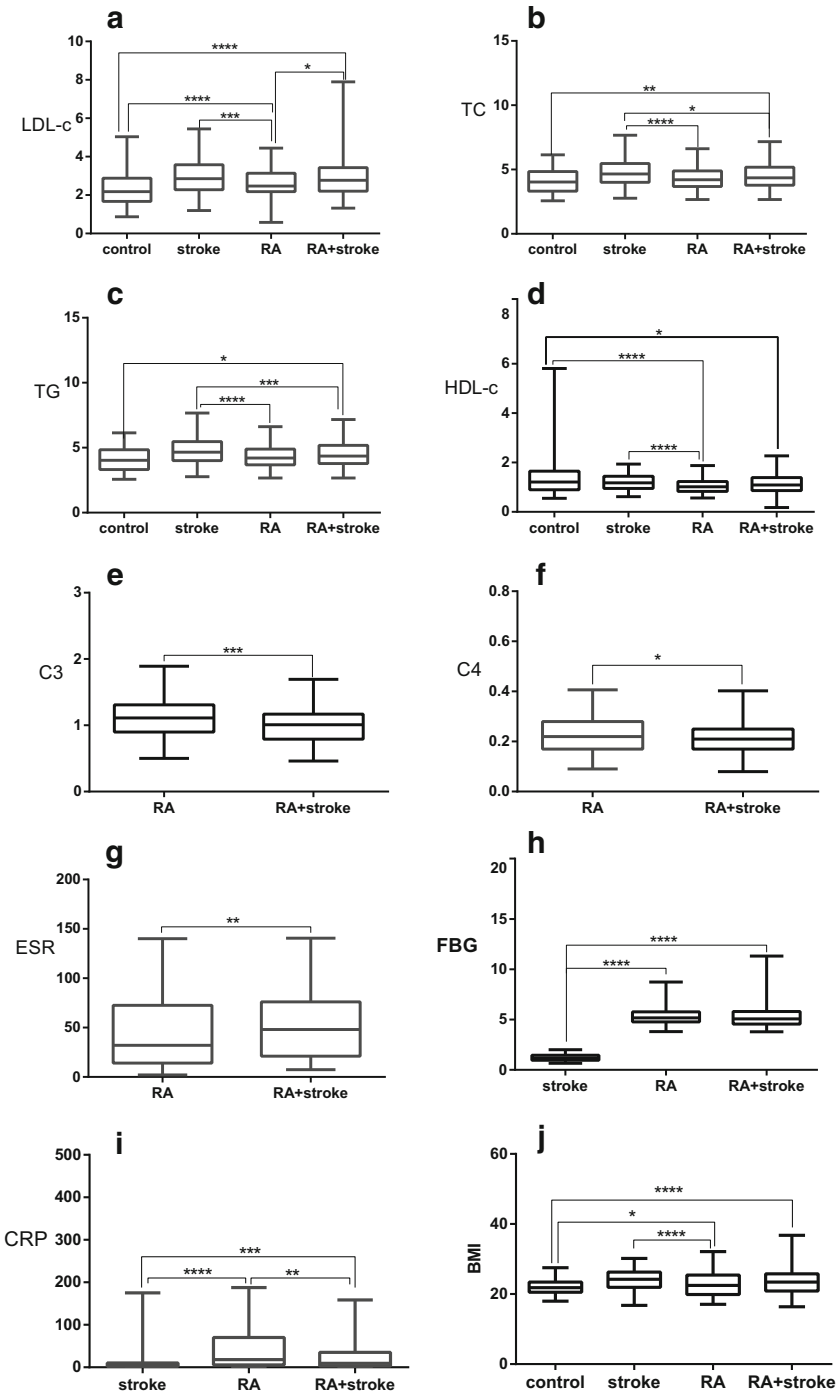

Fig. 2 Comparison of lipid profile, Serologic profile et al. parameters among four groups by using Kruskal–Wallis one-way analysis of variance (ANOVA), subsequently, using post hoc Dunn's multiple comparison test (A-J: LDL-C, TC, TG, HDL-c, C3, C4, ESR, GLU, CRP, BMI). Values were expressed as medium, 25–75 percentile and 2.5–97.5 percentile. LDL_C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; HDL_C, high-density lipoprotein cholesterol; C3, complement 3; C4, complement 4; ESR, erythrocyte sedimentation rate; FBG, fasting blood glucose; CRP, C-reactive protein; BMI, body mass index. Significance between two group: **P* value < 0.05; ***P* value < 0.01; ****P* value < 0.001; *****P* value < 0.0001

stroke group were significantly higher as compared to the health control group ($P < 0.0001$). Meanwhile, the FBG level was significantly increased ($P < 0.001$) in the RA+stroke and RA groups compared to the stroke group, but no significant differences were observed for the RA+stroke and RA groups (Fig. 2h).

Comparison of inflammatory markers and serological status between RA patients with and without stroke

There was no significant difference in the positivity rate of anti-CCP antibodies between the RA+stroke group and RA group ($\chi^2 = 1.593$, $P = 0.207$); the positivity rate of RF in RA+stroke group was significantly higher than that in the RA group (80.13% vs. 66.28%, $P < 0.05$) and stroke group (80.13% vs. 6.86%, $P < 0.0001$), as presented in Table 2. In addition, the levels of C3, C4, and CRP were significantly lower in the RA+stroke group than those in the RA group (C3: $P < 0.001$, Fig. 2e; C4: $P < 0.05$, Fig. 2f; CRP: $P < 0.001$, Fig. 2i). Notably, the levels of CRP and ESR were significantly elevated in the RA+stroke group than in the stroke group ($P < 0.001$ and $P < 0.01$, respectively; ESR: Fig. 2g).

Exploring the association between lipid levels, inflammatory markers, and risk of stroke among RA patients

Clinically relevant baseline variables that had a univariate relationship with outcome entered the binary logistic regression model. Variables for inclusion were carefully chosen, given the number of events available, to ensure parsimony of the final model. All results are shown in Fig. 3. In the final model of the RA+stroke group versus the RA group, the independent risk factors for stroke development in RA patients were listed as ESR ≥ 20 mm/h (OR = 5.39 (2.52, 11.55), $P < 0.0001$),

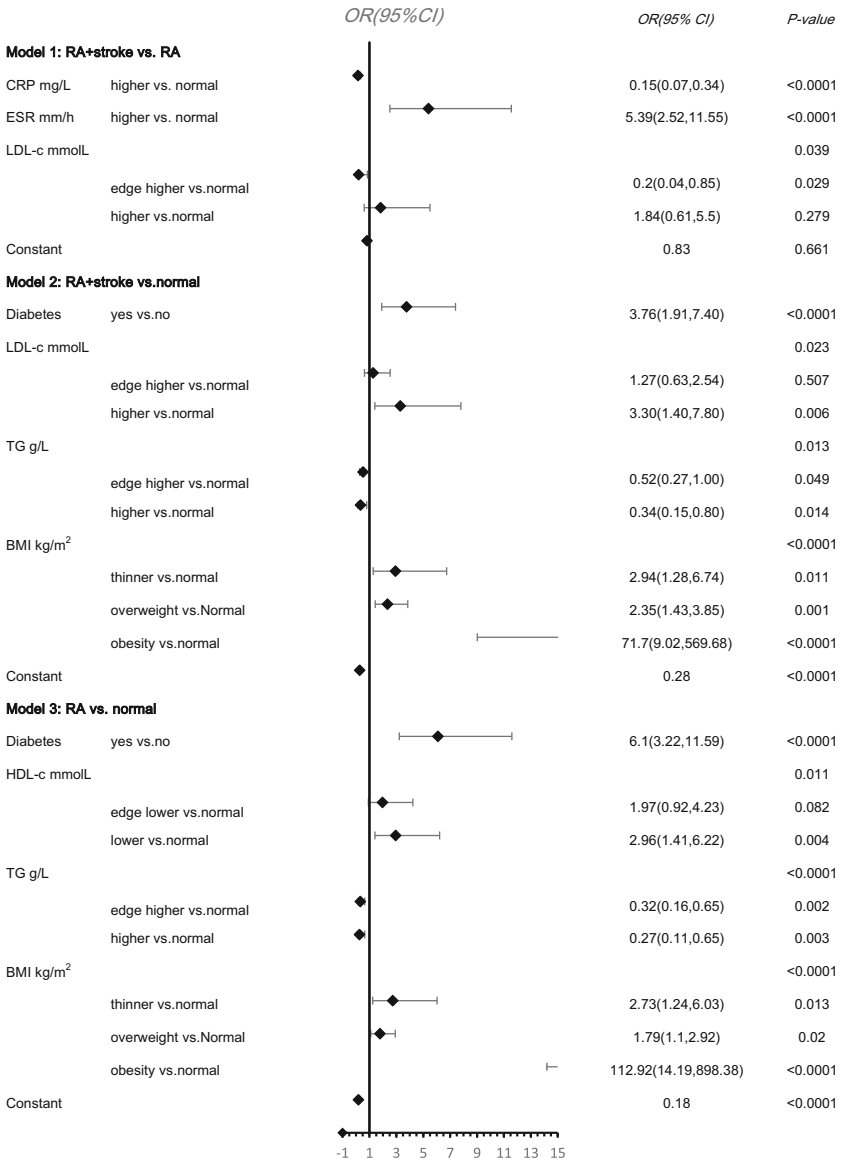

Fig. 3 Multivariable logistic regression analysis for the risk factors among RA with stroke patients. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HDL_C, high-density lipoprotein cholesterol; LDL_C, low-density lipoprotein cholesterol; RA, rheumatoid arthritis; TC, total cholesterol; TG, triglycerides; BMI, body mass index; OR, odds ratios; 95% CI, 95% confidence intervals

LDL-C ≥ 3.4 and < 4.1 mmol/L (OR = 0.2 (0.04, 0.85), P = 0.029), LDL-C ≥ 4.1 mmol/L (OR = 1.84 (0.61, 5.5), P = 0.279), and CRP ≥ 8 mg/L (OR = 0.15 (0.07, 0.34), P < 0.0001). In the final model of the RA+stroke group versus

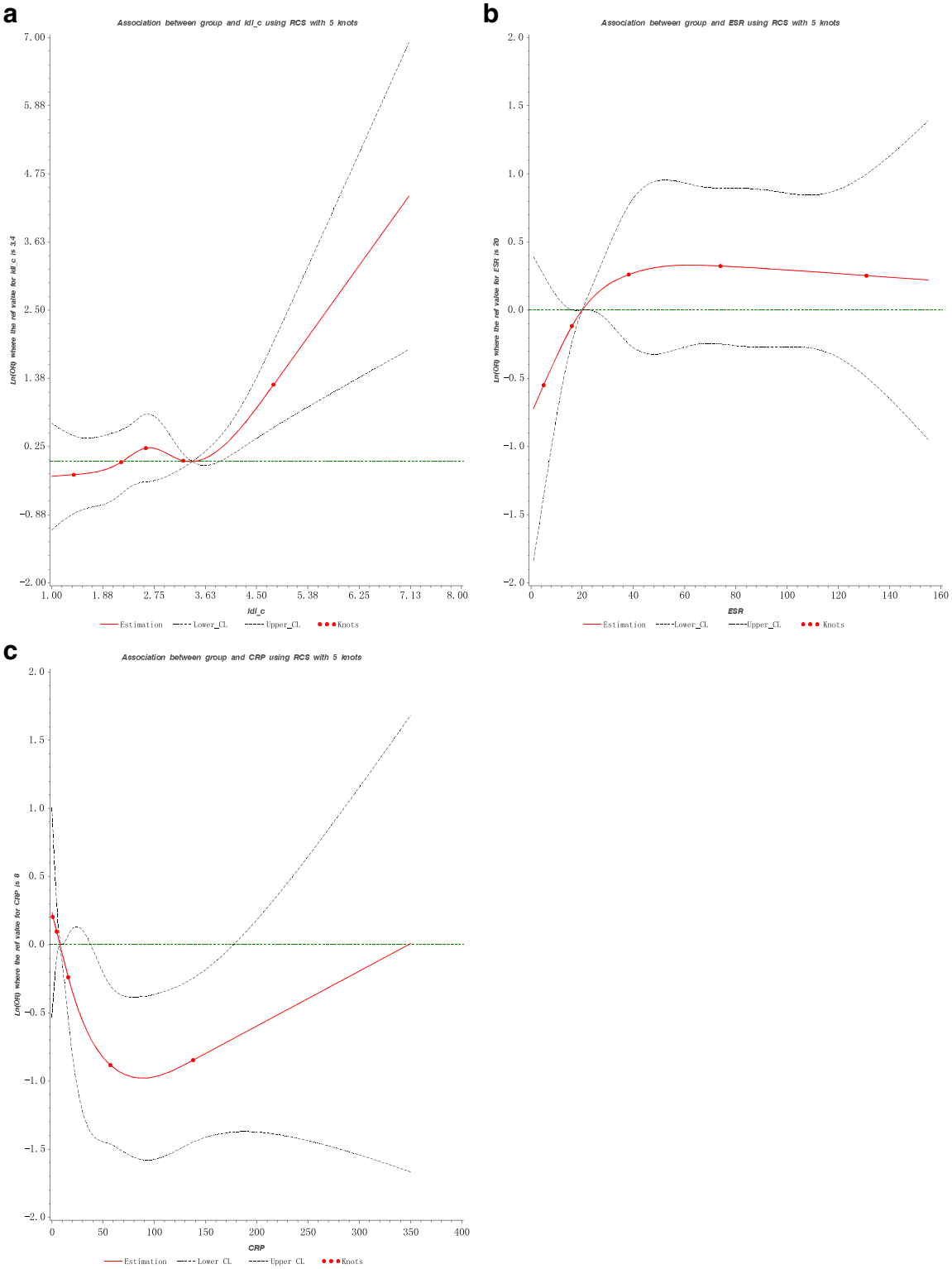

Fig. 4 Spline regression curve fitted with the binary logistic regression model between **a** LDL-c, **b** ESR, and **c** CRP and risk of stroke among RA Patients. *Y*-axis indicates the ln (OR) of stroke for any value of LDL-c, ESR, or CRP compared with the reference values. Dashed lines refer to 95% confidence intervals, Lower_CL, lower confidence limit; Upper_CL, upper confidence limit. LDL_C, low-density lipoprotein cholesterol; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; OR, odds ratios

the health control group, the significant risk factors were found to be diabetes (OR = 3.76 (1.91, 7.40), $P < 0.0001$), LDL-C ≥ 4.1 mmol/L (OR = 3.30 (1.40, 7.80), $P = 0.006$), TG ≥ 1.70 (OR = 0.52 (0.27, 1.00), $P = 0.049$), TG ≥ 2.30 g/L (OR = 0.34 (0.15, 0.80), $P = 0.014$), and the abnormal level of BMI. In the final model of the RA group versus the health control group, the risk of RA patients was associated with HDL-C < 1.04 mmol/L (OR = 2.96 (1.41, 6.22), $P = 0.004$), diabetes (OR = 6.1 (3.22, 11.59), $P < 0.0001$), TG ≥ 1.70, and ≥ 2.30g/L (OR = 0.32 (0.16, 0.65), $P = 0.002$; OR = 0.27 (0.11, 0.65), $P < 0.003$; respectively) and higher BMI.

Dose-response analysis of the association between lipid levels, inflammatory markers, and risk of stroke among RA patients

The results of both univariate and multivariate analyses revealed the levels of LDL-C, CRP, and ESR were significantly different between RA patients with and without comorbid stroke. The association between LDL-C, CRP, ESR levels and stroke development in RA patients was further evaluated using restricted cubic splines. We selected five nodes (5th, 25th, 50th, 75th, 95th percentile), using ESR = 20 mm/h, CRP = 8 mg/L, and LDL-C = 3.40 mmol/L as reference values to plot a dose-response curve combined with a binary logistic regression model.

Linear dose-response association

As shown in Fig. 4, our results indicated a significant linear association between LDL-C level, ESR level, and risk of comorbid stroke among RA patients (Fig. 4a: LDL-C, $P_{\text{lin-association}} = 0.091$; Fig. 4b: ESR, $P_{\text{lin-association}} = 0.253$). For LDL-C level, the risk of stroke development among RA patients was reduced until to 2.1 mmol/L, exhibited an increasing trend in the range of 2.61 to 3.40 mmol/L, and began rising dramatically at 3.40 mmol/L. For ESR level, when the level of ESR was elevated (≥ 20 mm/h), the risk of stroke in RA patients was increased exponentially at first and then ascended gradually until reaching a plateau (steady state).

Nonlinearity dose-response association

A similar upturned funnel-shaped association was found between serum CRP level and the risk of stroke among RA patients, with significant nonlinearity ($P_{\text{nonlin-association}} = 0.0073$; Fig. 4c). RA patients had a lower risk of developing stroke at approximate 80 mg/L CRP level (OR = 0.45 (0.25, 0.84)), while CRP level > 230 mg/L could increase the risk of stroke in RA patients, although no significant difference was observed between the RA+stroke and RA groups. By considering the CRP level of 8 mg/L as the reference value, we found a decreased risk of stroke by 48% ($OR_{50} = 0.48$ (0.27, 0.88), $P < 0.05$) and 49% ($OR_{100} = 0.49$ (0.26, 0.91), $P < 0.05$) among RA patients, with every 50 and 100 mg/L increased of CRP levels. When the CRP level was 250 mg/L, the risk of stroke in RA patients increased by 20% ($OR_{250} = 1.20$ (0.38, 3.76), $P > 0.05$), suggesting that much higher CRP levels may increase the risk of stroke development among RA patients, shown as Fig. 5.

Discussion

To the best of our knowledge, this study is the first to examine the metabolic abnormalities between RA and stroke in Chinese population. Our results mainly indicated that RA patients with stroke exhibited much higher levels of CRP, ESR, and LDL-C than RA patients. For dyslipidemia, our findings revealed that RA patients with stroke have a higher rate of diabetes, higher level of LDL-C and BMI, and lower TG level compared to the healthy, while a higher HDL-C and lower TG level but not a higher LDL-C level were detected among RA patients compared with the healthy. Presumably, increased LDL-C level played a pivotal role in promoting the development of stroke in patients with RA. Furthermore, both linear and nonlinear dose-response associations were found between these biochemical parameters and the risk of comorbid stroke among RA patients.

Previous studies have reported that RA is a risk factor for CVD [18], independently of traditional CVD risk factors such as age, gender, smoking, diabetes, hypercholesterolemia, hypertension, sedentary lifestyle, and family history of early coronary artery disease [19]. Among the different subtypes of CVD, the prevalence of stroke in RA patients increased by 1.64 times [20]. Likewise, the prevalence of ischemic stroke was 2.66 times higher in RA patients than in general population [20]. Therefore, it is important to investigate the serum biochemical markers that could predict the risk of stroke among RA patients.

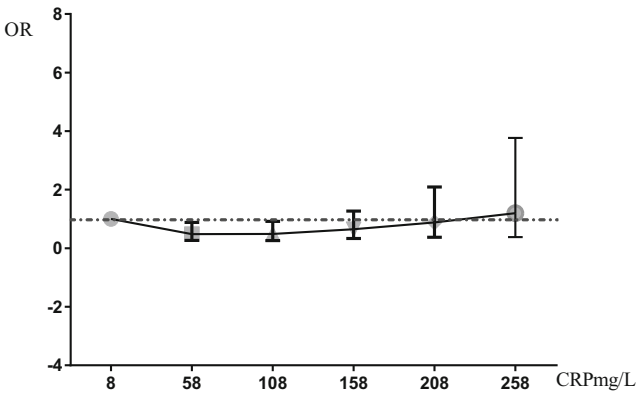

Fig. 5 The risk of stroke among RA Patients with each 50mg/L increase in CRP level compared with RA without stroke patients. Abbreviation: CRP, C-reactive protein; *OR*, odd ratios

Dyslipidemia may play a critical role in determining CVD [11]. However, several studies [21, 22] have reported a U-shaped relationship, in which RA patients with lower LDL cholesterol level tended to develop CVD and stroke, as similar to RA patients with high LDL-C levels, termed the "lipid paradox." The findings of our study revealed that higher LDL-C levels could increase the risk of comorbid stroke among RA patients. In addition, the occurrence of diabetes, lower HDL-C level, and higher BMI could serve as the independent risk factors for RA patients. A nonlinear and complex association between LDL-C level and CVD risk (including myocardial infarction and ischemic stroke) was observed in RA cohorts [11]. Conversely, our results indicated a significant linear dose-response association between LDL-C and stroke risk in RA patients. Taken altogether, a consistent OR value change was observed across two different types of analyses, and hence, a high LDL-C level may confer an increased risk to stroke in RA patients. Comparing model 1, model 2, and model 3, besides finding that increased LDL-C level played a pivotal role in promoting the development of stroke in RA patients, we also found that the BMI level of stroke without RA patients and that in RA patients were higher than the general healthy population; the TG distribution proportion of stroke without RA patients and that in RA patients was lower than in the general healthy population, while the average level of TG of which was higher than that in the general healthy population. What's similar is that Katherine P. Liao and Jun Liu also reported the high mean triglyceride levels in RA patients compared to non-RA controls [21].

Inflammatory processes play an essential role in the acceleration of CVD risk and mortality in RA patients [11, 23]. Elevated levels of CRP and ESR can independently predict the radiographic progression of joint disease as well as increased disability and worsen outcomes in RA [24, 25]. Our study indicated the importance of elevated ESR and CRP levels, in the development of stroke among RA patients. A similar J-shaped linear association was observed between ESR level and stroke risk in RA patients, indicating that higher ESR level can accelerate the development of stroke among RA patients. Increasing evidence suggests that elevated ESR may promote carotid artery intimal-medial thickness in RA patients and healthy individuals [26], and contribute to a higher rate of cardiovascular death [27]. In our study, a similar upturned funnel-shaped nonlinearity association was found between serum CRP level and the risk of stroke among RA patients, manifesting that higher CRP level can lead to an increasing risk of stroke in RA patients. The acute-phase reactant CRP in RA patients [28] is an inflammatory marker associated with increased cardiovascular risk [29] and is an important risk factor for atherosclerosis in chronic inflammatory conditions during RA [11, 30, 31]. Additionally, Taoshou reported that serum CRP level was substantially associated with the plaque of atherosclerosis, while long-term high CRP level can trigger an inflammatory response on vascular endothelial cells [32]. Atherosclerosis has been well recognized as an independent risk factor for stroke [33]. Therefore, it is not surprising that higher elevated level of CRP is an independent risk factor for stroke among RA patients [31].

This retrospective study could not manifest significance difference on long-term use of traditional DMARDs and biologic DMARDs between RA with and without stroke patients, in accordance with the results of Audrey S. L., Low AS, Greenberg JD etc. [20, 34, 35]. However, some studies have reported that traditional DMARDs and biologic DMARDs appeared to modify the risk of stroke in RA. Some studies suggested that methotrexate [36, 37] and hydroxychloroquine [38] were associated with decreased incident stroke in RA patients and other studies suggested that biologic DMARDs, tocilizumab raised concern for a possibly increased risk of stroke [39] and tumor necrosis factor inhibitors [40, 41], had been associated with decreased clinical stroke and the risk decreases further with long-term use [40] in RA. The above results are not always consistent. The relationship between DMARDs and stroke remain to be validated in the real-world setting.

The study bridged the gap examining lipid subtypes and individual contributions of ESR vs. CRP among patients with RA. The subjects in this study were optimally matched by using the PSM to balance the confounders (age and sex). It is clear that stroke and CHD are highly correlated, thus, our study excluded CHD patients to avoid strengthening and then merely emphasizing the association of RA with stroke. We selected the first laboratory test results of first admission due to stroke among RA+stroke patients to reduce the impact of different treatments among the study groups, especially the use of statin and insulin drugs. However, certain limitations are inevitable in this study. First, all subjects in this study were from an EMR, while the outpatient cases should have been included to generate a more comprehensive view of the phenomenon being studied. Second, the accuracy of cigarette-smoking history, alcohol-drinking history, and menstrual history might be affected, as the data collected were from EMR, and thus, the results should be interpreted with caution. Third, lipid profiles are routinely examined among the inpatients in China; CRP, ESR, RF, and anti-CCP are merely routinely examined in RA patients; CRP is routinely examined in stroke patients; partial tests of participants were unavailable. Finally, the patients' metabolic indexes in this study should have been collected prior to the first stroke event ideally, but reason of the data collected was from EMR; we collected the first admission data for stroke in RA patients.

In summary, our findings underlined the importance of systemic inflammation and demonstrated the complicated role of dyslipidemia for the risk of stroke in patients with RA. Thus, more attention should be paid to RA patients with

increased levels of ESR, LDL-C, and CRP, for the prevention of stroke comorbidity. In addition, these findings can facilitate the treatment of RA and prevent stroke development among RA patients. Notably, a close monitoring is required for RA patients with dyslipidemia and elevated inflammatory markers, and the primary stroke preventive strategies should be directed against these risk factors. Further investigation with more delicate study design and larger sample size is warranted to confirm our original findings or predict the risk of stroke among RA patients and select treatment schedule.

Contributors FRX analyzed and interpreted the data and drafted the manuscript. LYF designed the study. FRX, TTW, HNL, YWX and MC collected the data. LYF contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content and approved the final version of the manuscript. All authors have read and approved the final manuscript. FRX and LYF were the study guarantors.

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Compliance with ethical standards

Disclosures None.

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