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1 **Association of Erythrocyte Fatty Acid Profiles with the Presence and Rupture of**
2 **Intracranial Aneurysms**

3

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45 ABSTRACT

46 Background

47 Risk stratification for intracranial aneurysm (IA) rupture remains suboptimal.
48 Disrupted lipid metabolism may contribute to IA development and rupture. As stable
49 biomarkers of long-term lipid status, evaluation of erythrocyte fatty acids may aid in
50 risk assessment, although their clinical relevance remains unclear.

51

52 Methods

53 This case-control study included 175 participants (64 controls without IAs, 61 with
54 unruptured IAs, and 50 with ruptured IAs) who were recruited in 2024. Twenty-two
55 erythrocyte fatty acids were quantified by gas chromatography, and their associations
56 with IA presence and rupture were assessed using logistic regression. Fatty acids
57 associated with rupture were identified using least absolute shrinkage and selection
58 operator (LASSO) regression and incorporated into established rupture risk models
59 (PHASES, ELAPSS, and UCAS). Incremental discriminatory value was evaluated by
60 comparing the change in the area under the receiver operating characteristic (ROC)
61 curve (Δ AUC) using DeLong's test. Validation was performed in an independent
62 external cohort comprising 53 participants (27 with unruptured IAs and 26 with
63 ruptured IAs).

64

65 Results

66 High erythrocyte levels of total n-3 polyunsaturated fatty acids (PUFAs) were

67 associated with decreased IA risk (OR 0.28, 95% CI 0.17–0.46), whereas high levels
68 of saturated fatty acids, monounsaturated fatty acids, n-6 PUFAs and trans fatty acids
69 were associated with increased IA risk (all $P < 0.01$). Total n-3 PUFA (OR 0.57, 95%
70 CI 0.36–0.91; $P = 0.019$) and n-6 PUFA (OR 1.81, 95% CI 1.14–2.87; $P = 0.012$)
71 levels were also associated with rupture. Five key fatty acids identified by LASSO
72 (C18:1, C20:2n-6, C20:4n-6, C20:5n-3, C22:6n-3) significantly improved rupture
73 discrimination (Δ AUC 0.134–0.163; all $P < 0.05$). In the validation cohort, fatty acid
74 integration similarly enhanced discrimination across all risk models (all $P < 0.05$).

75

76 Conclusions

77 Erythrocyte fatty acid profiles are associated with IA presence and rupture.
78 Incorporation of these profiles into existing risk models has the potential to refine
79 rupture risk prediction and inform individualized risk stratification, pending validation
80 in prospective or longitudinal cohorts.

81

82 **Running Title:** Erythrocyte Fatty Acids and Aneurysm Status

83 **Keywords:** intracranial aneurysm; fatty acids; subarachnoid hemorrhage;
84 erythrocytes; case–control studies

85

86 BACKGROUND

87 Intracranial aneurysms (IAs) are focal dilations of cerebral arteries that affect
88 approximately 3% of the global population [1]. Rupture of these aneurysms results in
89 subarachnoid hemorrhage (SAH), a life-threatening condition associated with
90 significant morbidity and mortality [2,3]. Advances in noninvasive imaging have
91 increased the detection of unruptured IAs (UIAs). Despite their prevalence, the
92 rupture rate of UIAs is low. Only approximately 0.25% of patients with UIAs
93 eventually experience rupture [4,5]. This discrepancy poses a clinical dilemma: while
94 most UIAs remain stable, a small subset of these aneurysms has a substantial risk of
95 rupture. Accurate risk stratification is therefore essential to weigh preventive
96 treatment risks against rupture outcomes and to inform management decisions.

97

98 To support clinical decision-making, several rupture risk stratification tools have been
99 developed, including the PHASES [6], ELAPSS [7], and UCAS [8] scores. However,
100 these tools rely mainly on morphological and demographic factors, overlook
101 biological variables, and show limited predictive accuracy in external validations [9–
102 13]. These limitations highlight the need for the use of more reliable and biologically
103 informed biomarkers to refine rupture risk assessment and optimize management
104 strategies for patients with UIAs.

105

106 Emerging evidence suggests that disturbances in lipid metabolism contribute to IA
107 pathogenesis and progression [14]. Histopathological studies have revealed distinct

60

108 differences in the fatty acid compositions of the walls of ruptured and unruptured IAs.

109 Even in the presence of normal circulating lipid levels, lipids accumulate in the
110 aneurysm wall, are taken up and oxidized by mural cells, and may contribute to cell
111 loss, degeneration of the wall, and eventual rupture [15]. Dysregulated arachidonic
112 acid (AA) metabolism has also been observed in ruptured aneurysm walls and may
113 promote local inflammation via the PGE_2 – EP_2 – $\text{NF-}\kappa\text{B}$ pathway [16,17]. Similarly, a
114 prospective cohort study reported that plasma oleic acid (OA) and AA levels were
115 associated with aneurysm instability [18].

116

117 However, the specific variations in fatty acid profiles among patients with ruptured
118 IAs (RIAs), UIAs, and controls without IAs remain poorly characterized. Moreover,

66

119 measurements of the levels of fatty acids in plasma or serum are influenced by
120 short-term fluctuations, limiting their ability to capture long-term metabolic status.
121 Erythrocyte fatty acids, in contrast, have recently emerged as stable, long-term
122 biomarkers of fatty acid status [19]; they exhibit lower variability and greater
123 reproducibility than do the fatty acids in plasma and serum and are minimally
124 influenced by diet [20,21]. The clinical utility of measuring the fatty acids present in
125 erythrocytes has been demonstrated in several cardiovascular diseases, including
126 myocardial infarction [22], heart failure [23], ischemic stroke [24], and peripheral
127 arterial disease [25,26]. Given these advantages, erythrocyte fatty acids may provide a
128 more stable metabolic fingerprint associated with IA stability or rupture.

129

This study aimed to characterize erythrocyte fatty acid profiles in patients with IAs, investigate their associations with IA presence and rupture, and evaluate whether the use of fatty acids as markers could improve discrimination between ruptured and unruptured aneurysms. Clarifying these relationships may enhance risk stratification, inform dietary and therapeutic interventions, and facilitate biologically informed risk prediction in clinical practice.

METHODS

This study aimed to examine the associations between erythrocyte fatty acid profiles and IA presence and rupture. The study protocol was approved by the institutional review board. All participants provided written informed consent before taking part in the study.

Study population and data collection

From January to December 2024, the study consecutively enrolled newly diagnosed IA patients, including incidental and symptomatic cases, and controls without IAs at the study institution. IA diagnosis was confirmed by computed tomography angiography. Patients were grouped into UIA and RIA categories. Aneurysm rupture was determined by two senior physicians on the basis of clinical presentation (e.g., severe headache, vomiting, altered consciousness) and CT evidence of SAH consistent with the aneurysm location. In patients with multiple aneurysms, rupture was attributed to a single lesion based on clinical and imaging findings unless the

152 rupture site could not be definitively identified. Control participants were
153 consecutively recruited from individuals who underwent routine MRA at the same
154 centers and during the same period as IA patients (convenience sampling) (**Figure**
155 **S1**).

156

157 The exclusion criteria included the following:

13 158 (1) use of n-3 polyunsaturated fatty acid (PUFA) supplements within the past 6
159 months;

160 (2) presence of nonsaccular aneurysms;

62 161 (3) prior diagnosis of cerebral arteriovenous malformation, moyamoya disease, dural
162 arteriovenous fistula, cavernous hemangioma, or severe cerebral atherosclerosis (>70%
163 stenosis);

13 164 (4) history of polycystic kidney disease, Ehlers–Danlos syndrome, Grönblad–
165 Strandberg syndrome, or Marfan syndrome;

166 (5) pregnancy; and

167 (6) samples deemed unsuitable for analysis (e.g., samples with hemolysis, coagulation,
168 or chylous blood).

169

16 170 Demographic and clinical data were collected via structured questionnaires and
171 face-to-face interviews.

172

173 **Blood collection**

Each participant provided a 5-mL fasting venous blood specimen collected in tubes containing dipotassium ethylenediaminetetraacetic acid. Blood samples from IA patients were collected prior to any intervention, surgery, or pharmacological treatment; samples from control participants were collected before their routine magnetic resonance angiography scans. Erythrocytes were separated from whole blood by centrifugation at $1,790 \times g$ for 10 min at 4 °C within 2 hours after sampling and then stored at -80 °C until further analysis. All the samples were handled in a way that avoided multiple freeze-thaw cycles, and all the measurements were performed within one year after collection.

183

Analysis of erythrocyte fatty acids

Erythrocyte fatty acids were measured according to the method of Harris et al. [27]. Fatty acid methyl esters (FAMES) were prepared from erythrocytes using the acid transesterification method [28] and identified by gas chromatography (Agilent GC 6890, Agilent, California, USA). Quantification was performed using heptadecanoic acid as an internal standard. Case and control samples were processed together in a single batch by blinded laboratory staff. FAMES were separated on a DB-5MS capillary column (30 m×0.25 mm×0.25 µm; Agilent, California, USA) with helium (purity >99.999%) as the carrier gas, and individual fatty acids were identified by matching their retention times to those of commercially available standards (Nu-Check Prep, Minnesota, USA). The assays showed high reproducibility, with intra-assay coefficients of variation below 5%. All values are reported as percentages

196 of the total identified fatty acids.

197

198 The levels of 22 individual erythrocyte fatty acids and three fatty acid indices,
199 including the n-3 index, the n-6:n-3 ratio, and the AA:EPA ratio (arachidonic acid to
200 eicosapentaenoic acid ratio), were measured as described in previous studies [28–30].

201 The fatty acids and their characteristics are listed in **Table 1**.

202

203 **Statistical analysis**

204 Participants were classified into two sets of groups: (1) IA (RIA and UIA) and no-IA
205 groups to assess fatty acids associated with aneurysm presence, and (2) RIA and UIA
206 groups to assess fatty acids associated with aneurysm rupture. Group differences were
207 analyzed using Student's t test, the Mann–Whitney U test, or the chi-square
208 test/Fisher's exact test, as appropriate.

209

210 Univariable logistic regression was used to estimate odds ratios (ORs) and 95%
211 confidence intervals (CIs) for the association between erythrocyte fatty acid levels per
212 standard deviation (SD) increase and the presence or rupture of IAs. Multivariable
213 logistic regression were then applied, adjusting for potential confounding factors. The
214 minimally adjusted model included age, sex, and body mass index (BMI); the fully
215 adjusted model included those parameters as well as education level, smoking status,
216 alcohol use status, and history of diabetes, hypertension, coronary artery disease, and
217 ischemic stroke. In these models, continuous variables were modeled as continuous,

218 whereas categorical variables were modeled as categorical. Covariate selection was
219 informed by prior literature and clinical relevance [5,28,31]. Multicollinearity among
220 covariates was assessed using the variance inflation factor (VIF); no evidence of
221 multicollinearity was observed (all the VIFs were <5). In addition, fatty acid levels
222 were categorized into tertiles, and the associations of the high and low tertiles with IA
223 presence and rupture were examined, providing clinically meaningful effect estimates.

224 Subgroup analyses were conducted according to age (≤ 60 vs. >60 years) and sex.
225 Interaction effects were assessed using likelihood ratio tests to compare models with
226 and without interaction terms. Sensitivity analyses were conducted in which the data
227 for participants with significant metabolic or cardiovascular comorbidities (diabetes,
228 coronary artery disease, and ischemic stroke) were excluded. Nonlinear associations
229 were evaluated using restricted cubic spline (RCS) functions with knots at the 10th,
230 50th, and 90th percentiles.

231

232 To identify key fatty acids associated with rupture, least absolute shrinkage and
233 selection operator (LASSO) regression was applied. Aneurysm rupture risk scores
234 (PHASES, ELAPSS, and UCAS) were calculated and used in conjunction with the
235 levels of selected fatty acids in logistic regression models to differentiate RIA from
236 UIA. Prior to LASSO regression, all erythrocyte fatty acid values were standardized
237 (mean = 0, SD = 1) to ensure the comparability of the penalty coefficients across the
238 variables. The optimal penalty parameter (λ) for LASSO regression was determined
239 via 10-fold cross-validation using the one-standard-error rule applied to the minimum

binomial deviance. This approach helps prevent overfitting and selects the most predictive fatty acids, thereby enhancing model robustness. Model performance was assessed using receiver operating characteristic (ROC) curves; AUCs were compared using DeLong's test, with 95% confidence intervals derived from 2000 bootstrap resamples. To enhance clinical interpretability, the net reclassification improvement (NRI) was used to evaluate whether adding fatty acid values to traditional models at the optimal cutoff improved the proportion of patients correctly reclassified into more appropriate risk categories. Model calibration was assessed using Hosmer–Lemeshow tests and calibration plots. Additionally, decision curve analysis (DCA) was performed to assess clinical utility. DCA quantifies the net benefit across different threshold probabilities, balancing true-positive and false-positive rates for treatment decisions.

An independent validation set of 53 patients (27 with UIAs and 25 with RIAs) was collected between January and April 2025 from Beijing Chaoyang Hospital, using the same inclusion and exclusion criteria that were used with the primary cohort. Owing to the limited availability of external cases, this cohort served as a proof-of-concept validation for assessment of the generalizability of the findings. The sample processing, baseline characteristics, and fatty acid analysis protocols were consistent with those used in the primary cohort. Both cohorts were analyzed in the same laboratory by the same trained personnel using identical chromatographic conditions, with blinding to clinical grouping. To minimize batch effects, an identical internal

262 standard (heptadecanoic acid) was added to all the samples, and the peak areas were
263 normalized to correct for injection volume and instrument drift. The same batch of the
264 internal standard and the calibration standards was used in all runs to ensure
265 consistency. The independent test set was not involved in model development and was
266 exclusively used to evaluate the predictive performance of selected fatty acid values
267 and combined models in distinguishing patients who experienced ruptured aneurysms
268 from those whose aneurysms did not rupture (RIA vs. UIA). The coefficients obtained
269 from the training set were applied to the test set without re-estimation, allowing for an
270 unbiased evaluation of model performance. Baseline characteristics for the training
271 and test sets are summarized in Table S1.

272

273 Due to the exploratory nature of the study and the intercorrelated fatty acid measures,
274 no adjustment for multiple comparisons was made, and the observed associations
275 should be interpreted with caution [32–34]. All tests were two-sided, with $P < 0.05$
276 considered to indicate statistical significance. Statistical analyses were performed in R
277 (version 4.4.0). The glmnet (v4.1-8), pROC (v1.18.5), rms (v7.0-0), nricens (v1.6),
278 and ResourceSelection (v0.3-6) packages were used for LASSO regression,
279 ROC/AUC analysis, restricted cubic spline modeling, NRI estimation, and Hosmer–
280 Lemeshow calibration testing, respectively. All the analytical code and deidentified
281 data used in this study are available from the corresponding author upon reasonable
282 request.

283

RESULTS

Comparison of the erythrocyte fatty acid profiles of the IA and no-IA groups

A total of 175 participants (mean age 58.3 ± 9.8 years, 66.9% female) were included, comprising 111 patients with IAs (51 ruptured, 60 unruptured) and 64 controls without IAs. The baseline characteristics of sex, BMI, education, smoking status, alcohol use status, and medical history were similar in the two groups. However, the IA group was older (59.4 ± 9.3 vs. 56.3 ± 10.4 years, $P = 0.041$) and had a higher incidence of hypertension (62.2% vs. 32.8%, $P < 0.001$). No participant had a prior history of SAH (Table 2).

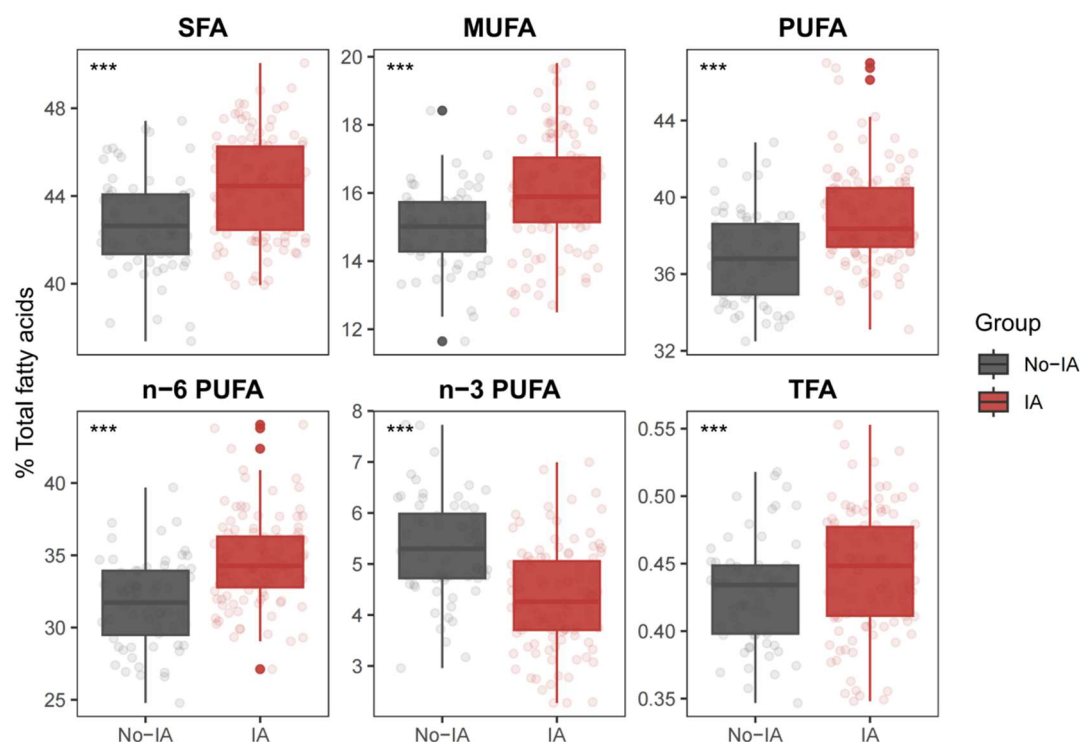
Significant differences in erythrocyte fatty acid profiles were observed between the IA and no-IA groups (Figure 1 and Table 3). Both minimally adjusted and fully adjusted models yielded nearly identical associations. In the fully adjusted model, higher total SFAs (OR 2.49 per SD increase, 95% CI 1.61–3.83; $P < 0.001$), MUFAs (OR 3.12 per SD increase, 95% CI 1.92–5.07; $P < 0.001$), n-6 PUFAs (OR 3.59 per SD increase, 95% CI 2.11–6.12; $P < 0.001$), and TFAs (OR 1.81 per SD increase, 95% CI 1.22–2.69; $P = 0.003$) were positively associated with IA risk, whereas total n-3 PUFAs were inversely associated with IA risk (OR 0.28 per SD increase, 95% CI 0.17–0.46; $P < 0.001$).

Among the individual SFAs, C16:0, C18:0, C20:0, C22:0, and C24:0 were positively associated with IA risk, whereas C14:0 was not. Among the MUFAs, C18:1, C20:1,

and C24:1 were positively associated with IA risk, whereas C16:1 was not. All individual n-6 PUFAs were positively associated with IA risk. Among TFAs, only C16:1n-7t showed a significant positive association. Among the n-3 PUFAs, only C22:6n-3 was inversely associated with IA risk, whereas C18:3n-3 and C20:5n-3 were not significantly associated with it (Table 3 and Figure S2).

In terms of fatty acid indices, the n-3 index was inversely associated with IA risk (OR 0.26 per SD increase, 95% CI 0.15–0.43; $P < 0.001$), whereas the n-6:n-3 ratio was positively associated with IA risk (OR 5.18 per SD increase, 95% CI 2.68–10.00; $P < 0.001$). The AA:EPA ratio was not significantly associated with IA risk (Table 3 and Figure S2).

Figure 1. Differences in erythrocyte fatty acid composition between IA and no-IA participants. Comparisons represent raw group differences. Statistical significance was assessed using the Mann–Whitney U test. *** $P < 0.001$; ** $P < 0.01$; * $P < 0.05$; ns, not significant.



321

2

322 Abbreviations: IA, intracranial aneurysm; SFAs, saturated fatty acids; MUFAs, monounsaturated fatty
 323 acids; PUFAs, polyunsaturated fatty acids; TFAs, trans fatty acids.

324

67

325 Similar results were observed when fatty acids were categorized into tertiles for
 326 comparison of groups with high levels versus groups with low levels (Table S2). The
 327 associations between fatty acid levels and IA risk were consistent across age and sex
 328 strata, with no significant interaction effects observed (Figures S3 and S4). The
 329 associations between key fatty acids and IA risk remained consistent even after
 330 exclusion of participants with significant metabolic or cardiovascular comorbidities
 331 (Table S3). RCS analyses revealed mostly linear relationships, except in the case of
 332 total MUFAs, which showed a J-shaped association with risk ($P_{nonlinear} = 0.020$)
 333 (Figure S5). IA risk remained stable below 15% MUFAs and then increased

334 markedly.

335

336 **Comparison of erythrocyte fatty acid profiles in the UIA and RIA groups**

6 337 After differences in fatty acid levels between the IA and no-IA groups were
338 established, their associations with aneurysm rupture risk were evaluated. Among the
339 111 IA patients (mean age 59.4 ± 9.4 years; 72.1% female) with 140 aneurysms, 60 had
9 340 UIAs, and 51 had RIAs. The baseline characteristics of the two groups were similar.
341 Multiple aneurysms were present in 21.8% of the patients (Table 4).

342

343 Of the 140 aneurysms, ruptured lesions were more frequently located in the
344 C7/Acha/Pcom (46.2%), Acom (28.8%), and M1/M2 (11.5%) segments, whereas
345 unruptured aneurysms were primarily located at C6 (27.3%), C7/Acha/Pcom (25.0%),
346 and M1/M2 (17.0%). Compared with UIAs, RIAs had a greater prevalence of
347 irregular shape and daughter sacs (all $P < 0.001$), but the difference in size between
348 UIAs and RIAs was not significant (median [IQR]: 4.70 [4.00–6.05] mm for RIA vs.
349 4.26 [3.15–5.48] mm for UIA; $P = 0.120$). PHASES, ELAPSS, and UCAS scores
40 350 were significantly higher in the ruptured group (all $P < 0.05$).

351

49 352 According to the fully adjusted models, total SFA, MUFA and TFA levels were not
353 significantly associated with aneurysm rupture risk. In contrast, higher total PUFA
354 levels were associated with increased rupture risk (OR 1.63 per SD increase, 95% CI
355 1.05–2.55, $P = 0.030$), primarily driven by total n-6 PUFAs (OR 1.81 per SD increase,

95% CI 1.14–2.87, $P = 0.012$), whereas higher total n-3 PUFA levels were associated with reduced risk (OR 0.57 per SD increase, 95% CI 0.36–0.91, $P = 0.019$) (Figure 3, Table 5 and Figure S6).

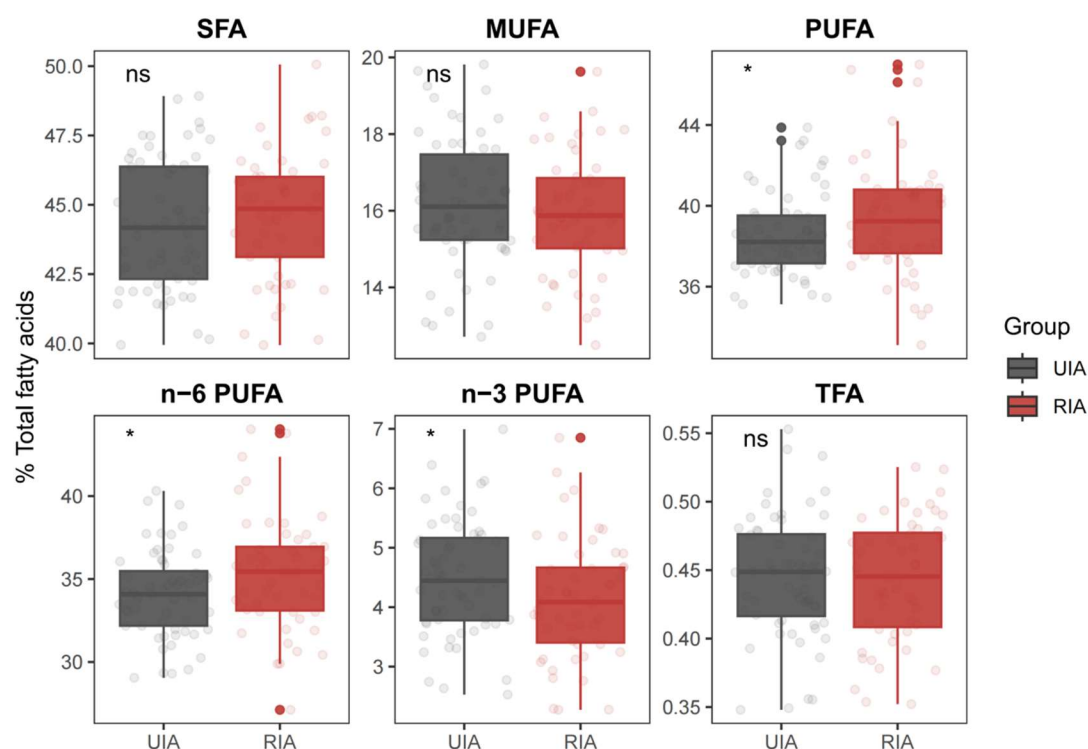
Among the individual n-6 PUFAs, C20:2n-6 (OR 1.68 per SD increase, 95% CI 1.05–2.70, $P = 0.031$), C20:4n-6 (OR 1.95 per SD increase, 95% CI 1.23–3.08, $P = 0.004$), and C22:5n-6 (OR 1.64 per SD increase, 95% CI 1.05–2.56, $P = 0.030$) were positively associated with rupture risk, whereas C18:2n-6, C18:3n-6, C20:3n-6, and C22:4n-6 were not significantly associated with rupture risk (Table 5 and Figure S6).

Among individual n-3 PUFAs, C22:6n-3 consistently exhibited an inverse association with rupture risk (OR 0.46 per SD increase, 95% CI 0.28–0.76, $P = 0.003$), as it did with aneurysm presence, whereas C20:5n-3 showed a positive association with rupture risk (OR 1.76 per SD increase, 95% CI 1.08–2.86, $P = 0.023$), possibly reflecting differences in the biological roles of individual n-3 PUFAs; no significant association was observed for C18:3n-3.

In terms of fatty acid indices, the n-3 index was inversely associated with rupture risk (OR 0.55 per SD increase, 95% CI 0.34–0.88; $P = 0.013$), whereas the n-6:n-3 ratio was positively associated with it (OR 2.08 per SD increase, 95% CI 1.23–3.52; $P = 0.006$) (Table 5 and Figure S6).

Similar results were observed when fatty acid levels were categorized into tertiles to facilitate comparison of high versus low groups (Table S4). These associations were consistent across both age and sex subgroups. Additionally, the associations between key fatty acids and IA risk remained consistent after participants with significant metabolic or cardiovascular comorbidities, including diabetes, coronary artery disease, and ischemic stroke, were excluded (Table S5). Restricted cubic spline analyses revealed linear trends (Figures S7 and S8).

Figure 3. Differences in erythrocyte fatty acid composition between UIA and RIA participants. The comparisons represent raw group differences. Statistical significance was assessed using the Mann-Whitney U test. *** $P < 0.001$; ** $P < 0.01$; * $P < 0.05$; ns, not significant.



Abbreviations: UIA, unruptured intracranial aneurysm; RIA, ruptured intracranial aneurysm; SFAs,

391 saturated fatty acids; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids; TFAs,
392 trans fatty acids.

393

394 **Identification of key fatty acids that distinguish ruptured and unruptured**
395 **intracranial aneurysms and model construction**

396 The discriminative value of erythrocyte fatty acid differences between participants
397 with UIAs and those with RIAs was then evaluated. Using LASSO regression
398 ($\lambda=0.061$), five key erythrocyte fatty acids—C18:1, C20:2n-6, C20:4n-6, C20:5n-3,
399 and C22:6n-3—were selected as a basis for distinguishing the presence of RIAs
400 (**Figure 4, A–C**). When integrated with the PHASES, ELAPSS, or UCAS scores,
401 including the levels of these fatty acids significantly improved model discrimination
402 in the training set (Δ AUC 0.134–0.163; all $P < 0.05$; **Figure 4D**) and in an
403 independent validation cohort (Δ AUC 0.202–0.218; P range 0.010–0.025; **Figure 4E**).
404 Moreover, including fatty acids in the model improved patient reclassification,
405 yielding NRI values ranging from 0.308 to 0.331 in the training set and from 0.262 to
406 0.308 in the test set (**Table S6**). Notably, the UCAS-fatty acid model showed the best
407 discriminative performance in the test set (AUC 0.851, 95% CI 0.762–0.939), with
408 sensitivity and specificity of 0.818 and 0.808, respectively, at the Youden index–
409 optimized threshold (0.342). All the models demonstrated good calibration, with
410 nonsignificant Hosmer–Lemeshow test results ($P > 0.05$) (**Figure S9 and Table S7**).
411 DCA revealed that compared with the traditional clinical model, the fatty acid
412 integration model demonstrated a superior net benefit over a broad range of treatment

threshold probabilities (**Figure S10**). These results suggest that incorporation of fatty acid biomarkers into the rupture risk model may support more accurate identification of ruptured aneurysms in clinical decision-making.

Figure 4. Identification of key fatty acids associated with rupture risk and model construction. A: Five

key fatty acids were identified from a total of 52 clinical and fatty acid variables using least absolute shrinkage and selection operator (LASSO) regression. All five of the selected fatty acids are known to

influence vascular inflammation, endothelial function, and membrane stability. These fatty acids were

then integrated into three established aneurysm rupture risk models (PHASES, ELAPSS, and UCAS) to

construct combined models. The performance of the integrated models was compared with that of the

original clinical models, and the discriminatory ability of the integrated models was further validated in

an independent external test set. B: LASSO coefficient profile plots against $\log(\lambda)$. The optimal λ based

on the minimum error criterion was used to select variables with nonzero coefficients. C: Tenfold

cross-validation and minimum error criteria were applied to identify the optimal penalization

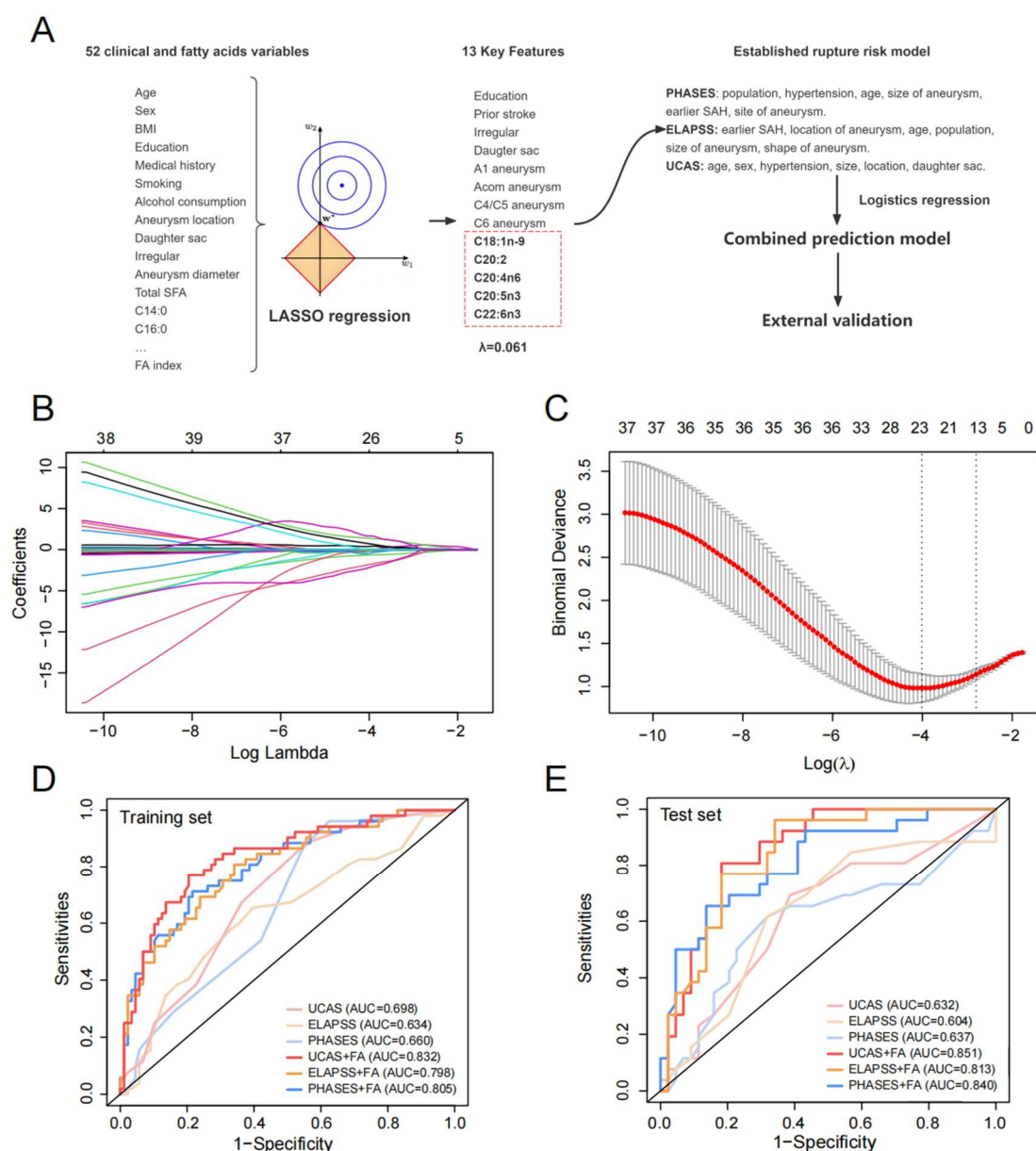
coefficient. The left dashed vertical line represents the optimal λ values when the minimum error

criterion is applied, whereas the right dashed vertical line represents the optimal λ values when one

standard error of the minimum criterion is applied. D: Receiver operating characteristic curves for the

clinical model and the integrated clinical–fatty acid model in the training set. E: Receiver operating

characteristic curves for the clinical model and the integrated clinical–fatty acid model in the test set.



432

433 Abbreviations: LASSO, least absolute shrinkage and selection operator; SFA, saturated fatty acid; FA,

434 fatty acid; AUC, area under curve.

435

436 DISCUSSION

437 This study provides evidence that compared with controls without IAs, patients with

438 IAs exhibit distinct differences in erythrocyte fatty acid composition. Specifically, IA

439 patients had elevated levels of SFAs, MUFAs, n-6 PUFAs, and TFAs and reduced

440 levels of n-3 PUFAs. An imbalance marked by increased n-6 and decreased n-3
441 PUFAs was associated with IA rupture, indicating a role of disrupted fatty acid
442 metabolism in aneurysm formation and progression. These compositional differences
443 may influence vascular remodeling and inflammatory responses via endothelial and
444 immune cell pathways. However, associations between the levels of specific fatty
445 acids and aneurysm status were not corrected for multiple comparisons; thus, these
446 results are exploratory and need further validation.

447
448 Among the lipids showing significant differences, five fatty acid markers (C18:1,
449 C20:2n-6, C20:4n-6, C20:5n-3, and C22:6n-3) were identified that, when
450 incorporated into established rupture risk scores (PHASES, ELAPSS, and UCAS),
451 significantly improved predictive performance. Notably, compared with serum or
452 plasma measures used in previous studies, erythrocyte membranes reflect long-term
453 dietary and lipid status, whereas serum levels of fatty acids fluctuate acutely. These
454 characteristics highlight the potential utility of erythrocyte fatty acid profiling as a
455 tool for individualized rupture risk assessment.

456
457 To the knowledge of the authors of this paper, few studies have investigated the
458 relationship between erythrocyte fatty acid levels and IA status. Previous
459 investigations have largely focused on serum fatty acids [18]; thus, the present work
460 addresses this critical gap. Among its key findings, the association of elevated
461 erythrocyte AA (C20:4n-6) levels with both IA presence and rupture is of particular

interest. AA and its downstream metabolites—including prostaglandins, leukotrienes, and thromboxanes—are well-documented mediators of inflammation, oxidative stress, and endothelial dysfunction, all of which have been implicated in IA pathogenesis [17,26,35–37]. The concordance of the present results with earlier research linking AA to aneurysm instability underscores the possibility that modulation of AA metabolism may offer a therapeutic avenue for preventing IA progression [18].

AA is derived primarily from dietary sources of n-6 PUFAs, particularly animal-based foods [38]. Increasing n-6 PUFA intake in populations, as observed in China in recent decades, may contribute to elevated AA levels [39]. Consistent with this trend, most n-6 PUFAs were associated with increased IA risk, although only specific subtypes (e.g., AA, C20:2n-6, and C22:5n-6) were linked to rupture. Interestingly, this pattern differs from the findings of some cardiovascular studies, which have reported that dietary intake or circulating concentrations of certain subtypes of n-6 PUFAs (mainly C18:2n-6 (linoleic acid, LA)) may be associated with reduced cardiometabolic risk and favorable profiles of lipids, inflammation, insulin resistance, blood pressure, and body composition [40–42]. LA is considered an essential fatty acid, as humans cannot synthesize it, and it plays a critical role in early development [43,44]. Whether other subtypes of n-6 PUFAs exert similar protective effects remains unclear. Overall, these findings indicate that different n-6 PUFA subtypes may play distinct biological roles, highlighting the need for further subtype-specific investigations in cerebrovascular and aneurysm research.

484

485 In contrast to previous reports that associated lower OA (C18:1) levels with aneurysm
486 instability [18], higher erythrocyte OA levels in IA patients were observed in this
487 study. This discrepancy may, on one hand, result from differences in study design,
488 sample type, the dietary patterns of the studied population, or analytical methods; on
489 the other hand, it reflects the importance of considering OA sources. While dietary
490 OA intake and supplementation have demonstrated anti-inflammatory and
491 cardioprotective effects, plasma OA levels are only weakly correlated with dietary
492 intake ($r = 0.05$), suggesting that circulating OA is largely derived via de novo
493 lipogenesis from fatty acid precursors [45,46]. Specifically, OA (18:1) is synthesized
494 from saturated stearic acid (18:0) via the enzymatic activity of stearoyl-CoA
495 desaturase-1 (SCD-1). Therefore, elevated OA levels may reflect upstream
496 dysregulation of fatty acid metabolism rather than dietary intake. Metabolic shifts that
497 occur in this way may not necessarily confer cardiovascular benefits [45,47,48].
498 SCD-1 has been shown to play a key role in triglyceride synthesis and is implicated in
499 the development of insulin resistance and obesity [49,50]. These findings underscore
500 the necessity for mechanistic studies that clarify the OA's role in IA development.

501

502 A novel finding of this study is that there is an inverse association between total n-3
503 PUFA levels—especially C22:6n-3 (docosahexaenoic acid, DHA)—and IA risk. DHA
504 is the predominant long-chain n-3 PUFA in erythrocyte membranes, accounting for
505 approximately 70–90% of total n-3 PUFAs (approximately twice the level of

506 C20:5n-3), and it exerts well-established vascular protective effects. Prior studies of
507 patients with aortic aneurysms have shown that DHA supplementation reduces
508 inflammation and arterial stiffness [31,51,52]. Mechanistically, DHA enhances
509 endothelial nitric oxide synthase activity and nitric oxide production, thereby
510 modulating ion channel function (e.g., transient receptor potential vanilloid 4 and
511 L-type calcium channels) and improving vascular tone regulation and endothelial
512 shear stress responses [53]. Additionally, DHA activates the FFAR4 and PPAR- γ
513 pathways, triggering Nrf2-mediated antioxidant responses and inhibiting the NF- κ B
514 inflammatory cascade. These mechanisms may help attenuate inflammatory processes
515 within the aneurysm wall and mitigate subsequent mural degradation [54–61].
516 Although DHA can be endogenously synthesized from alpha-linolenic acid (ALA,
517 C18:3n-3), the conversion rate is low (<5%), which may explain the lack of a
518 significant association between ALA and IA risk in the current study [62].

519

520 In contrast, the role of C20:5n-3 (eicosapentaenoic acid, EPA) appears to be more
521 complex. While some experimental studies suggest protective effects [63], in this
522 study higher endogenous EPA levels were associated with increased rupture risk. This
523 discrepancy may reflect differences between the effects of exogenous
524 supplementation and endogenous metabolism, dose- and tissue-specific effects, or
525 functional differences between EPA and DHA [64–69]. Specifically, EPA and DHA
526 differ in their incorporation into membrane phospholipids and lipid rafts, which are
527 cholesterol- and sphingolipid-enriched liquid-ordered microdomains (10–200 nm) that

528 act as important signaling platforms. DHA preferentially integrates into lipid rafts,
529 altering membrane organization, protein activity, and receptor clustering, whereas
530 EPA undergoes less pronounced raft incorporation [70]. Additionally, both of these
531 fatty acids compete with AA for cyclooxygenase and lipoxygenase enzymatic activity,
532 thereby modulating eicosanoid profiles [71]. Notably, compared with EPA, DHA
533 appears to be more effective at suppressing the production of AA-derived
534 proinflammatory mediators and promoting the production of anti-inflammatory
535 resolvins, protectins, and maresins [72]. Allaire et al. compared the effects of EPA and
536 DHA supplementation on inflammatory markers in men and women at risk for
537 cardiovascular disease. Compared with EPA supplementation, DHA supplementation
538 led to a greater reduction in interleukin-18 levels and a greater increase in adiponectin
539 levels [73]. These results suggest that compared with EPA, DHA may have broader
540 anti-inflammatory effects. Additionally, unlike DHA, EPA has limited effects on blood
541 pressure regulation, a fact that may partially explain the differences in vascular
542 protection observed in the current study [74]. Clinical studies have also suggested that
543 a modest bleeding risk is associated with high-dose EPA supplementation [75]. These
544 findings are consistent with the observation reported herein that higher EPA levels are
545 associated with increased risk of aneurysm rupture. Overall, the current findings
546 highlight the complexity of EPA and DHA biology, and further studies are warranted
547 to elucidate their distinct roles in vascular inflammation and aneurysm rupture.

548

549 Higher levels of several SFAs (C16:0, C18:0, C20:0, C22:0, and C24:0) were also

550 found to be associated with IA risk. SFAs are known to promote inflammation and
551 endothelial dysfunction [76–78]. Similarly, despite regulatory efforts to reduce
552 exposure, TFAs remained elevated in IA patients, suggesting that even low levels may
553 adversely impact vascular integrity. However, elevated erythrocyte SFA and TFA
554 levels may not exclusively reflect dietary intake, as they can also be influenced by
555 endogenous synthesis and metabolic dysregulation. Further studies integrating dietary
69 556 assessment with erythrocyte fatty acid profiling are warranted to elucidate the
557 complex interplay between diet, metabolism, and IA risk.

558

10 559 In summary, IA patients exhibited erythrocyte fatty acid profiles that were distinctly
560 different from those of controls. The incorporation of five specific fatty acids into the
561 established rupture risk models significantly increased the predictive performance of
562 the models, with the AUC improving from 0.698 to 0.832, highlighting the
10 563 pathophysiological relevance of fatty acid metabolism and the potential of fatty acid
564 profiling as a biomarker-based adjunct for clinical risk stratification. If validated, such
565 profiling could augment imaging-based risk assessment, particularly in patients with
566 multiple small UIAs where clinical decision-making remains challenging. While
567 erythrocyte fatty acid profiles show promise as potential biomarkers for aneurysm risk
568 stratification, their causal or modifiable role in aneurysm pathophysiology remains to
19 569 be established. Further interventional or longitudinal studies are warranted to confirm
570 these findings and evaluate their clinical applicability.

571

572 Study strengths and limitations

573 The use of objective erythrocyte fatty acid biomarkers enhances this study, enabling
574 the detection of associations with aneurysm occurrence and rupture while indicating
575 their potential utility in risk prediction.

576

50 577 Several limitations should be acknowledged. First, as a case-control study, the
578 potential for reverse causation cannot be excluded. Reverse causation refers to the
579 possibility that the disease (aneurysm) may influence the measured exposures
580 (erythrocyte fatty acids) rather than the exposures contributing to the disease.

581 However, erythrocyte fatty acids reflect long-term lipid exposure and are minimally
582 influenced by short-term dietary fluctuations [79]. In individuals with stable dietary
583 habits, these profiles likely represent preexisting metabolic states rather than acute
584 responses to disease, thus reducing the risk of reverse causation and supporting their
585 potential utility as predictive biomarkers for aneurysm formation and rupture. Second,

45 586 this study recruited participants from tertiary hospitals in the Beijing region, which
587 may introduce selection bias and limit the generalizability of the findings. Regional
588 factors, such as dietary habits, socioeconomic status, access to health care, education
589 level, and genetic background, could influence both fatty acid metabolism and
590 aneurysm rupture risk, potentially leading to systematic differences between the
591 current study population and other cohorts. Third, the absence of detailed dietary

31 592 intake data limited the ability to directly assess the relationship between diet and fatty

73 593 acid composition. While the multivariable models were adjusted for major clinical

594 covariates (age, sex, hypertension, hyperlipidemia, diabetes, smoking) and excluded
595 patients with common metabolic or cardiovascular comorbidities in sensitivity
596 analyses, residual confounding by unmeasured lifestyle factors, medication use (e.g.,
597 statins, antihypertensives), or systemic inflammatory status remains possible. These
598 unmeasured factors could still influence fatty acid metabolism and affect the accuracy
599 of the association estimates. Fourth, no correction for multiple comparisons was
600 performed, indicating that the current findings should be considered exploratory and
601 warrant further confirmatory research. Finally, the relatively small sample size may
602 limit the generalizability of the findings. Future large-scale, multicenter prospective
603 cohort studies and randomized trials incorporating detailed dietary assessments are
604 needed to validate these results and guide clinical applications.

605

606 Conclusion

607 Erythrocyte fatty acid profiles differed significantly between IA patients and controls.
608 The incorporation of five fatty acids into established rupture risk models was
609 associated with improved predictive performance, suggesting that fatty acid
610 metabolism may be relevant to aneurysm instability and that erythrocyte fatty acid
611 profiling could serve as a useful adjunct to current risk stratification to support more
612 individualized surveillance and treatment strategies.

613

614 Abbreviations

615 AA, arachidonic acid

- 616 ALA, alpha-linolenic acid
- 617 AUC, area under the curve
- 618 BMI, body mass index
- 619 CI(s), confidence interval(s)
- 19 620 DHA, docosahexaenoic acid
- 621 EDTA, ethylenediaminetetraacetic acid
- 622 EPA, eicosapentaenoic acid
- 623 FAMES, Fatty acid methyl esters
- 624 IA(s), intracranial aneurysm(s)
- 21 625 LASSO, least absolute shrinkage and selection operator
- 53 626 MUFA(s), monounsaturated fatty acid(s)
- 627 OA, oleic acid
- 56 628 OR(s), odds ratio(s)
- 629 PUFA(s), polyunsaturated fatty acid(s)
- 630 RCS, restricted cubic spline
- 631 RIA(s), ruptured intracranial aneurysm(s)
- 44 632 ROC, receiver operating characteristic
- 633 SAH, subarachnoid hemorrhage
- 634 SD, standard deviation
- 47 635 SFA(s), saturated fatty acid(s)
- 636 TFA(s), trans fatty acid(s)
- 637 UIA(s), unruptured intracranial aneurysm(s)

638

15

639 **DECLARATIONS**

640 **Ethics approval and consent to participate**

641 This study adhered to the principles set forth in the Declaration of Helsinki and
642 received approval from the institutional ethics committee. All participants provided
643 written informed consent before taking part in the study.

3

644

645 **Consent for publication**

646 Not applicable.

647

648 **Availability of data and materials**

649 The datasets used and/or analyzed during the current study are available from the
650 corresponding author upon reasonable request.

651

652 **Competing interests**

653 The authors declare that they have no competing interests.

654

655 **Funding**

656 This work was supported by the National Natural Science Foundation of China (grant
657 numbers 82271319 and 8217050951) and the National Key R&D Program of China
658 (2022YFC2409601).

39

659

Authors' contributions

DW, XC, and SG designed the study. DW wrote the first draft of the manuscript. SG, JL, JJ, and LD collected clinical data, processed biological samples, and performed laboratory measurements and quality control. HG, XL, and YL critically revised the manuscript. ML, FM, and YL supervised the study and provided overall project coordination. All the authors read and approved the final manuscript.

Acknowledgments

Not applicable.

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