# Serum interleukin-1 is a new biomarker to predict the risk of rebleeding of ruptured intracranial aneurysm after admission

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# Abstract

Interleukin-1 (IL-1) could induce inflammation of the aneurysm wall, which might be related to intracranial aneurysm rupture. The aim of this study was to investigate whether IL-1 could serve as a biomarker to predict the risk of rebleeding after admission. Data between January 2018 and September 2020 were collected from patients with ruptured intracranial aneurysms (RIAs) and were retrospectively reviewed. The serum IL-1β and IL-1ra levels were detected using a panel, and IL-1 ratio was calculated as the $\log_{10}(\text{IL-1ra/IL-1β})$. The predictive accuracy of IL-1 compared with previous clinical morphology (CM) model and other risk factors were evaluated by the c-statistic. 538 patients were finally included in the study, with 86 rebleeding RIAs. The multivariate Cox analysis confirmed aspect ratio (AR) > 1.6 (hazard ratio (HR), 4.89 [95%CI, 2.76−8.64], P < 0.001), size ratio (SR) > 3.0 (HR, 2.40 [95%CI, 1.34−4.29], P = 0.003), higher serum IL-1β (HR, 1.88 [95%CI, 1.27−2.78], P = 0.002) and lower serum IL-1ra (HR, 0.67 [95%CI, 0.56−0.79], P < 0.001) as the independent risk factors for rebleeding after admission. According to the c-statistics, the IL-1 ratio had the highest predictive accuracy (0.82), followed by IL-1ra and IL-1β (0.80), AR > 1.6 (0.79), IL-1ra (0.78), IL-1β (0.74) and SR > 3.0 (0.56), respectively. Subgroup analysis based on AR and SR presented similar results. The model combining IL-1 ratio and CM model showed higher predictive accuracy for the rebleeding after admission (c-statistic, 0.90). Serum IL-1, especially IL-1 ratio, could serve as a biomarker to predict the risk of rebleeding after admission. Unique identifier: ChiCTR1900024406, retrospectively registered.

# Introduction

Aneurysmal subarachnoid hemorrhage usually threatens middle-aged and elderly people. Rebleeding after admission is a major risk factor for poor prognosis of ruptured intracranial aneurysms (RIAs), which may even lead to pre-treatment mortality [10; 11]. The rebleeding usually occurs within six hours after the initial hemorrhage, and it is crucial to identify patients at high risk of rebleeding because of limited medical resources in China, which may not allow timely surgery for all patients [23]. In our previous work, although certain clinical and morphological factors have been found to be associated with rebleeding after hospital admission [15], there are still potential factors contributing to the event.

Inflammation is key to the development of intracranial aneurysms [9; 25]. After an aneurysm rupture, the patients will suffer a severe inflammation storm caused by hemorrhage. Previous studies reported that inhibition of interleukin-1 (IL-1) prevented aneurysm rupture [20] and reduced inflammation after subarachnoid hemorrhage [7]. Notably, serum IL-1 level is correlated to aneurysm wall enhancement [16], and IL-1β plays an important role in pyroptosis as a proinflammatory factor [24]. Thus, we hypothesized that serum IL-1 could provide a proinflammatory condition for RIAs and also predict the risk of rebleeding after admission.

In this study, we prospectively collected blood samples from RIA patients to investigate the correlation between serum IL-1 levels and rebleeding after admission to identify the potential of serum IL-1 as a biomarker for post-admission rebleeding.

# Methods And Materials

## Study population

Prospective patients treated for RIAs were enrolled at our medical center from January 2018 to September 2020. The following inclusion criteria were employed in this study: (1) patient had an aneurysm rupture confirmed by computational tomography (CT), and underwent angiogram to identify the RIAs; (2) patients were admitted to our medical center within 12 hours upon the onset of aneurysm rupture, which presented with typical symptoms, such as sudden coma, and severe headache; (3) patient had complete or traceable clinical records. Patients with intracranial tumors and rheumatic diseases that can lead to an abnormal change in IL-1 [21; 27] were excluded from the study, as were patients with certain factors that may contribute to an abnormal RIA (e.g., the family history of RIAs, rheumatic diseases and polycystic kidney) [26]. Besides, the following exclusion criteria were also applied: (1) cerebrovascular malformation (e.g., brain arteriovenous malformation and cavernous malformation) or intracranial tumors; (2) family histories of RIAs, rheumatic diseases (i.e., lupus) or polycystic kidney; (3) RIAs as dissecting or thrombus aneurysms because their formation mechanisms are completely different from the saccular aneurysms; (4) multiple intracranial aneurysms, leading to difficulty in the identification of the source of initial hemorrhage or rebleeding; and (5) patients who had received special treatment for RIAs in other medical institutions before admission.

## Serum IL-1 examination and quality control

We collected blood samples at two time points, i.e., at admission and at the time of surgery (before anesthesia). For blood samples at admission, the average time interval between the presence of subarachnoid hemorrhage (by symptoms) and blood sample collection was 4.5 hours (range, 1.2–14.8 hours). All samples were centrifuged at 3000 rpm for 10 minutes within 3 hours of collection and then stored in the liquid nitrogen. Samples with obvious signs of hemolysis were considered disqualified. To ensure the sample quality, the detection of IL-1 would be performed within 30 days of sample collection.

Serum IL-1 level was measured using a cytokine panel (SPCKA-PS-005710, R&D Systems, Biotechne corporation, Shanghai, China). The panel was pre-incubated with the primary antibodies, consisting of IL-1β, IL-1ra (IL-1 receptor antagonist) and tumor necrosis factor α (TNF-α) (R&D Systems, Biotechne corporation, Shanghai, China). After dilution, washing and incubation according to the manufacturer's protocol, the samples were subsequently assayed using the Ella workstation (Biotechne corporation, Shanghai, China). The total time of the examination was about 10 min. The IL-1 ratio was calculated as the $\log_{10}$(IL-1ra/IL-1β).

## Identification of rebleeding

The primary endpoint was rebleeding after admission, identified on the basis of clinical (a sudden disorder of consciousness, or suddenly or gradually worsening neurological states after admission) and radiological findings (significant increase in blood in the subarachnoid, intracerebral, or intraventricular

blood on the CT examination after admission). Rebleeding events were identified by two experienced blinded neurosurgeons (PJ. Jiang and J. Wu, who have been practicing cerebrovascular neurosurgeons for more than 5 years) based on post-admission CT and medical records. The discrepancies were resolved by consulting a senior neurosurgeon (S. Wang, working as a cerebrovascular neurosurgeon for more than 15 years). The patients were allocated to a rebleeding group or a stable group according to the onset of rebleeding after admission. The time interval (hours) between admission and rebleeding or surgery was observed.

# Clinical information and Morphology assessment

We collected clinical information from electronic medical records with respect to age, gender, hypertension, dyslipidemia, diabetes mellitus, coronary heart disease (CHD) and transient ischemic attack (TIA)/ischemic stroke, Hunt-Hess grade at the admission, blood pressure at admission and before rebleeding/surgery.

Morphological characteristics were measured in accordance with our previous studies [14; 15]. Two blinded neurosurgeons (investigator 1 and investigator 2) independently measured the morphological features, and the discrepancies were solved by consulting a senior neurosurgeon (working as a neurointerventional surgeon for more than 15 years). In this study, aneurysm size, neck diameter, perpendicular height and diameter of parent artery were measured. An in-depth analysis of the mean measurements for each neurosurgeon was performed. Aspect ratio (AR) and size ratio (SR) was calculated according to the previous study [5]. According to the unruptured intracranial aneurysm treatment score [6], we categorized all RIAs as AR > 1.6 or AR ≤ 1.6, and SR > 3 or SR ≤ 3. An irregular shape was defined as small bleb(s) or secondary aneurysm(s) protruding from the aneurysm fundus or bi-/multi-lobular aneurysm fundus. Modified Fisher scale (mFS) and aneurysm location (anterior cerebral artery (ACA), anterior communicating artery (AcomA), middle cerebral artery (MCA), internal carotid artery (ICA), posterior circulation (PC)) were also recorded by the two investigators based on CTs at admission and angiographies.

# Perioperative management

On admission, CT scans were performed once per day, and considered in case of a sudden coma or progressive deterioration of neurological status. The goal was to reduce systolic blood pressure acutely to 120–140 mmHg [1; 4]. All patients in Hunt-Hess grade I-II would receive surgical intervention within 24 hours.

For patients with Hunt-Hess of grade III-V at admission, immediate intervention would not be recommended, but rather standard care following guidelines is used until the patient is suitable for surgical intervention [4]. However, an emergency intervention would be considered in case of neurological condition progressive deterioration. Surgical intervention was only considered when neurological status progressively deteriorates, or a rebleeding or a cerebral hernia was identified in the CT.

# Statistical analysis

Category variables were compared using the chi-square test or Fisher's exact test, and independent samples t-test and Mann-Whitney U test were conducted for continuous variables. Survival analysis was performed using the Kaplan-Meier model and log-rank test. The significant parameters in univariable analysis were then evaluated by the Cox regression model to identify the independent risk factors related to rebleeding after admission. Results were presented in the form of hazard ratio (HR), and 95% confidence intervals (CI) were also calculated. The predictive probability of the clinical + morphology model (CM model) was calculated according to our previous study [15]. In receiver operating characteristic curve analysis, the performance of the parameter predicting rebleeding was measured using the value of the c statistic, with the value above 0.7 being considered a promising predictive accuracy. Subgroup analyses were subsequently performed based on factors independently associated with postadmission rebleeding and factors that may influence serum IL-1 levels, including gender, hypertension, dyslipidemia, diabetes mellitus, the severity of intracranial hemorrhage (i.e., mFS), aneurysm size, Hunt-Hess grade and time from admission to rebleeding. To combine the predictive values of different parameters or different models, we calculated the probability of multiple parameters using the multivariate logistic model. The probability was then output and used for further analysis. Statistical analysis was performed using SPSS 24.0 (SPSS, Chicago, USA), with a two-sided $P < 0.05$ being statistical significance.

# Results

# Demographic and clinical characteristics

Among the 538 included patients (Fig. 1), there were 212 males, with ages ranging from 31 to 77 years. The rebleeding events occurred in 86 patients (16.0%) and 62 patients (11.5%) were transferred to our medical institution within 12 hours of initial bleeding. 151 patients (28.1%) received surgical intervention more than 12 hours after admission. The median observation time (from admission to surgery/rebleeding) was 10.5 (range, 1.2–56.0 hours). The demographic and clinical characteristics of all RIA patients are summarized in Table 1. The results showed that more patients with rebleeding RIAs had a history of hypertension ($P < 0.001$) and dyslipidemia ($P = 0.043$). 227 patients were identified as mFS I-II and 314 as mFS III-IV, with no statistical significance ($P = 0.308$). 29 patients with rebleeding RIAs and 167 patients with stable RIAs were categorized as Hunt-Hess III-V, whereas the difference had no significance ($P = 0.569$). After the standard care, there was no difference in the blood pressure between patients with and without rebleeding RIAs ($P = 0.734$). No significant difference was found in gender, age, diabetes mellitus, CHD and TIA/ischemic stroke (all $P > 0.05$).

Representative cases of rebleeding and stable RIA are shown in Fig. 2.**A**. 85 (15.8%) RIAs were sited in AcomA/ACA, 245 (45.6%) in ICA, 188 (34.9%) in MCA and 20 (3.7%) in PC, with no significance of location between stable and rebleeding RIAs. More rebleeding RIAs were located at the bifurcation ($P < 0.001$) and were irregular in shape ($P < 0.001$). The rebleeding RIAs also presented larger aneurysm size ($P < 0.001$), larger AR ($P < 0.001$) and larger SR ($P < 0.001$). Moreover, serum IL-1β levels were higher (P < 0.001) and serum IL-1ra levels were lower (P < 1.001) in rebleeding RIAs compared with stable RIAs before

and after rebleeding (Fig. 2.**B-C**). For patients with rebleeding RIAs, the serum IL-1β level was increased, but the serum IL-1ra level was decreased, before and after rebleeding (Fig. 2.**D**). However, the TNF-α had no significant difference between rebleeding and stable RIAs (**Supplemental Fig. 1**). The reproducibility of morphological parameters is shown in Table 2.

# IL-1 as a risk factor for rebleeding after the admission

The result of the survival analysis is summarized in Fig. 3.**A** (also shown in **Table 3**), revealing that hypertension (*P* < 0.001), bifurcation (*P* < 0.001), irregular shape (*P* < 0.001), aneurysm size (*P* < 0.001), AR > 1.6 (*P* < 0.001), SR > 3.0 (*P* < 0.001), serum IL-1β level (*P* < 0.001) and serum IL-1ra level (*P* < 0.001) were significant risk factors for the rebleeding rate after admission. As shown in Fig. 3.**B**, univariate Cox analysis also demonstrated hypertension, bifurcation, irregular shape, aneurysm size, AR > 1.6, SR > 3.0, serum IL-1β and serum IL-1ra were correlated with the rebleeding after admission. A multivariate Cox analysis was further conducted based on the above risk factors (**Table 4**), confirming AR > 1.6 (HR, 4.89; 95%CI, 2.76−8.64; *P* < 0.001), SR > 3.0 (HR, 2.40; 95%CI, 1.34−4.29; *P* = 0.003), higher serum IL-1β (HR, 1.88; 95%CI, 1.27−2.78; *P* = 0.002) and lower serum IL-1ra (HR, 0.67; 95%CI, 0.56−0.79; *P* < 0.001) as the independent risk factors related to rebleeding after admission. The adjusted results were similar to the crude results.

# IL-1 as a predictor for rebleeding after the admission

The predictive accuracy of IL-1 for rebleeding after admission was further investigated. The IL-1 ratio was calculated based on the serum IL-1β and serum IL-1ra. The rebleeding RIAs showed a lower IL-1 ratio compared with the stable RIAs (see **Table 1**, *P* < 0.001). According to the c-statistic (Fig. 4.**A**), the IL-1 ratio had the highest predictive accuracy (0.82), followed by IL-1ra (0.78) and IL-1β (0.74). The comparison of the predictive accuracy among independent risk factors is presented in Fig. 4.**B**. Notably, the IL-1 ratio had higher accuracy compared with the IL-1β & IL-1ra, although the difference was not significant (*P* = 0.332). To further exclude the effect of AR and SR on the predictive accuracy of IL-1 for rebleeding after admission, we further performed subgroup analysis. As shown in **Fig. 5. A-B**, the IL-1β, IL-1ra and IL-1 ratio were still significantly related to the rebleeding after admission in each subgroup (all *P* < 0.05). Moreover, for each subgroup, the IL-1 ratio had the highest predictive accuracy for the rebleeding after admission (Fig. 5. **C-D**). Therefore, it is hypothesized that IL-1 may be a predictor of post-admission rebleeding.

# Subgroup analysis and predictive model

Subgroup analysis was performed based on Hunt-Hess grade and time before rebleeding/surgery to exclude the effect of the treatment time on the risk of rebleeding after admission. Compared with the patients with stable RIAs, patients with rebleeding RIAs had a lower IL-1 ratio at each Hunt-Hess grade (Fig. 5. **E**) and at each time interval before rebleeding/surgery (Fig. 5. **F**) (all *P* < 0.05). The Cox regression analysis based on each time interval and Hun-Hess grade also showed IL-1 ratio was associated with a low risk of rebleeding after admission (Fig. 5. **G**). Moreover, to exclude the effect of unmodified factors related to rebleeding and that may be associated with serum IL-1, we further performed subgroup

analysis (Fig. 6, and also seen in **Supplemental table 1**) and the results showed that the IL-1β, IL-1ra and IL-1 ratio were significant in each subgroup (all $P < 0.05$).

In our previous work, a clinical + morphology model (CM model) was established to evaluate the risk of rebleeding after admission. We further compared the predictive accuracy of IL-1 ratio, CM model and their combination (Fig. 7.**A**), with the combined model having the highest predictive accuracy (c-statistic, 0.90), followed by CM model (c-statistic, 0.85) and IL-1 ratio (c-statistic, 0.82), as presented in **Fig. 7.B**.

## Discussion

Identification of patients at high risk of post-admission rebleeding helps in the decision-making process during clinical treatment. This study revealed that the serum levels of IL-1β and IL-1ra may be significant risk factors for the rebleeding after admission, while the IL-1 ratio, calculated on the basis of serum IL-1β level and serum IL-1ra level, presented higher predictive accuracy for rebleeding after admission. In subgroup analyses, the IL-1 ratio still had good predictive accuracy for rebleeding while controlling for factors that may affect serum IL-1 levels. Thus, IL-1, especially IL-1 ratio, is speculated to be a novel biomarker to predict the risk of rebleeding of RIAs after admission.

Pyroptosis is a pro-inflammatory model of cell death involved in the development of various vascular diseases [3; 18; 29] and the formation of atherosclerosis [17]. Intracranial aneurysm rupture is the result of an imbalance between proinflammatory and anti-inflammatory factors [19]. Thus, if aneurysms indicate an unstable disease condition with severe inflammation infiltration, they are prone to rupture and hemorrhage. In this study, serum IL-1β and IL-1ra levels were found to be risk factors for rebleeding. At admission, patients with RIA who had higher IL-1β levels and lower IL-1ra levels had a higher risk of rebleeding. Serum IL-1β is an important mediator of pyroptosis and may induce new pyroptosis in other organs or regions, whose bioeffect can be antagonized by IL-1ra. Notably, serum IL-1 levels could reflect the inflammatory response of an individual under stress conditions (including subarachnoid hemorrhage) [13]. Although the IL-1 may come from various sources other than RIAs, the increasing serum IL-1β and lowering serum IL-1ra could provide a proinflammatory condition for RIAs, which might lead to a rebleeding after admission. Thus, the serum IL-1 level is correlated to the risk of rebleeding after admission.

The IL-1 ratio had a higher predictive accuracy compared with the single IL-1β and IL-1ra. As was already explained, the imbalance between pro- and anti-inflammatory chemicals is what causes the rupture. The bioeffects of IL-1β and IL-1ra are antagonistic [22]. The IL-1 ratio calculated by combining the IL-1β and IL-1ra could reflect the unbalance in an individual after an aneurysm rupture. Our data showed that a higher IL-1 ratio could indicate a lower risk of rebleeding in RIA patients. This phenomenon was also confirmed in subgroup with AR > 1.6 and subgroup with SR > 3.0. Additionally, the IL-1 ratio remained constant across all Hunt-Hess grades and pre-treatment intervals, which suggested that IL-1 ratio could accurately and consistently reflect the imbalance of proinflammatory and anti-inflammatory factors, and the inflammatory response of an individual after aneurysm rupture. Thus, IL-1 ratio might serve as a

biomarker to predict the risk of rebleeding after admission. For RIA patients with low IL-1 ratio, neurosurgeons should give surgical intervention as soon as possible, even though patients have high Hess-Hunt grades. However, if the surgical intervention can't be performed immediately, neurosurgeons should monitor apostasies (e.g., a sudden disorder of consciousness, or suddenly or gradually worsening neurological state). Furthermore, by employing the cytokine panel in this trial, we were able to immediately assist neurosurgeons in screening patients with a high risk of rebleeding by obtaining the IL-1 ratio in less than 10 minutes.

To exclude the effect of the factors related to serum IL-1 level, we performed subgroup analysis. Gender, which is related to estrogen receptors [2], may affect the inflammatory response, while dyslipidemia and diabetic mellitus are related to atherosclerosis and may lead to a change in serum IL-1 [8; 12; 28]. The severity of hemorrhage is also related to inflammatory response [30]. Notably, IL-1 ratio performed well in all subgroups except for the diabetic mellitus group, which could be caused by a small sample size of the diabetic mellitus subgroup (n = 4). Therefore, a larger sample size might be used to assess the importance of the IL-1 ratio in this demographic scenario.

Subsequently, we established a new model by adding the IL-1 ratio into our previous CM model [15]. We compared the predictive accuracy of each model, and the model including IL-1 ratio and CM model had the highest predictive accuracy for the rebleeding after admission. Therefore, a multidimensional predictive model should be further considered.

This study had some limitations First, even though the variables that may impact serum IL-1 levels were taken into account throughout the research, our findings could still be tainted by the possibility that additional comorbidities could affect changes in serum IL-1β and IL-1ra levels. Second, this study was conducted in the Chinese setting, so its generalizability may be constrained. Third, 62 patients were transferred from other hospitals to our medical institution within 12 hours of initial bleeding. As a result, we could overlook certain early rebleeding occurrences. Fourth, the study only took into account a small number of variables; nevertheless, additional confounding variables may potentially have an impact on the likelihood of rebleeding following admission. Despite the aforementioned restrictions, this study nonetheless demonstrated the potential of IL-1 as predictor for post-admission hemorrhage. To confirm our findings, detailed cohort studies and animal studies should be done.

## Conclusion

Serum IL-1 is upregulated in patients with rebleeding RIAs, before and after RIA rebleeding. IL-1 ratio could serve as a biomarker to predict the risk of rebleeding after admission and may be employed in the model to further improve the predictive accuracy.

## Glossary

RIA = ruptured intracranial aneurysm;

CT = computational tomography;

mFS = modified Fisher scale;

IL-1 = Interleukin-1;

mFS = Modified Fisher scale;

TIA = transient ischemic attack;

CHD = coronary heart disease;

AR = aspect ratio;

SR = size ratio.

# Declarations

## Ethics approval

The protocol of this work was approved by the Institutional Review Board of our institution (ky2017-076-01). Written informed consents were obtained from their legally authorized representatives.

## Availability of data and material

The data supporting the findings of this study are available from the corresponding author s upon reasonable request.

## Conflict of interest

The authors stated that they had no conflict of interest.

## Fundings

## Authors' contributions

Author contributions to the study and manuscript preparation include the following. Conception and design: Z.Wen. and QY. Liu. Acquisition of data: Z. Wen, QY. Liu, PJ. Jiang, J. Wu and JA. Li. Analysis and interpretation of data: Z. Wen, PJ Jiang. and QY. Liu. Drafting the article: Z. Wen, JP. Jiang and QY. Liu.

Critically revising the article: CC. Zhu and S. Wang. Approving the final version of manuscript on behalf of all authors: B. Ning. Study supervision: JA. Li and B. Ning.

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# Tables

Table.1. The demographic and baseline information of all RIA patients

| Characteristics | Stable RIAs n = 452 | Rebleeding RIAs n = 86 | P value |
|---|---|---|---|
| Male, n (%) | 172 (38.1%) | 40 (46.5%) | 0.142 |
| Age, years, m ± SD | 54.7 ± 10.4 | 53.9 ± 8.4 | 0.378 |
| Comorbidities, n (%) | | | |
| Hypertension | 151 (33.4%) | 49 (57.0%) | < 0.001† |
| Dyslipidemia | 37 (8.2%) | 13 (15.1%) | 0.043† |
| Diabetes mellitus | 16 (3.5%) | 4 (4.7%) | 0.618 |
| CHD | 10 (2.2%) | 3 (3.5%) | 0.480 |
| TIA/ischemic stroke | 13 (2.9%) | 4 (4.7%) | 0.389 |
| mFS at admission, n (%) | | | 0.308 |
| I-II | 195 (43.1%) | 32 (37.2%) | |
| III-IV | 257 (56.9%) | 54 (62.8%) | |
| Hunt-Hess grade at admission, n (%) | | | 0.569 |
| I-II | 285 (63.1%) | 57 (66.3%) | |
| III-V | 167 (36.9%) | 29 (33.7%) | |
| Blood pressure, n (%) | | | |
| At admission | | | 0.257 |
| < 160/90mmHg | 149 (33.0%) | 23 (26.7%) | |
| > 160/90mmHg | 303 (67.0%) | 63 (73.3%) | |
| Before rebleeding/surgery | | | 0.734 |
| < 140/80mmHg | 410 (90.7%) | 79 (91.9%) | |
| > 140/80mmHg | 42 (9.3%) | 7 (8.1%) | |
| Location, n (%) | | | 0.857 |
| AcomA/ACA | 68 (15.0%) | 17 (19.8%) | |
| ICA | 212 (46.0%) | 33 (38.4%) | |
| MCA | 157 (34.7%) | 31 (36.0%) | |
| PC | 15 (3.3%) | 5 (5.8%) | |

| Characteristics | Stable RIAs n = 452 | Rebleeding RIAs n = 86 | P value |
|---|---|---|---|
| Bifurcation, n (%) | 184 (40.7%) | 55 (64.0%) | < 0.001† |
| Irregular shape, n (%) | 75 (16.6%) | 47 (54.7%) | < 0.001† |
| Aneurysm size, mm, m (IQR) | 4.6 (3.8−6.7) | 6.8 (4.8−7.4) | < 0.001† |
| Aneurysm size | | | < 0.001† |
| < 5mm | 243 (53.8%) | 24 (27.9) | |
| 5-7mm | 100 (22.1%) | 20 (23.3%) | |
| 7-10mm | 73 (16.2%) | 36 (41.9%) | |
| > 10mm | 36 (8.0%) | 6 (7.0%) | |
| AR, m (IQR) | 1.2 (0.9−1.5) | 1.9 (1.4−2.3) | < 0.001† |
| AR > 1.6 | 80 (17.7%) | 60 (69.8%) | < 0.001† |
| SR, m (IQR) | 1.6 (1.2−2.4) | 2.3 (1.4-5.0) | < 0.001† |
| SR > 3.0 | 98 (21.7%) | 28 (32.6%) | < 0.001† |
| Serum IL-1β, $\times 10^2$ pg/ml, m (IQR) | 0.26 (0.18−0.39) | 0.44 (0.29−0.75) | < 0.001† |
| Serum IL-1ra, $\times 10^3$ pg/ml, m (IQR) | 4.25 (2.60−6.23) | 2.01 (1.70−2.71) | < 0.001† |
| IL-1 ratio, m (IQR) | 2.20 (1.92−2.41) | 1.57 (1.36−1.86) | < 0.001† |

┼, the parameter was significant.

RIAs, ruptured intracranial aneurysms; CHD, coronary heart disease; TIA, transient ischemic attack; mFS, modified Fisher scale; MCA, middle cerebral artery; ICA, internal carotid artery; AcomA, anterior communicating artery; ACA, anterior cerebral artery; PC, posterior circulation; AR, aspect ratio; SR, size ratio.

Table 2
Multivariate Cox analysis for rebleeding after admission

| Characteristics | Crude multivariate analysis | | | Adjusted multivariate analysis† | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | P value | HR | 95% CI | P value |
| Hypertension | 1.44 | 0.85−2.42 | 0.172 | | | |
| Bifurcation | 1.25 | 0.76−2.1 | 0.376 | | | |
| Irregular shape | 1.66 | 0.98−2.81 | 0.057 | | | |
| Aneurysm size | | | | | | |
| < 5mm | Reference | | | | | |
| 5-7mm | 0.88 | 0.47−1.65 | 0.684 | | | |
| 7-10mm | 1.71 | 0.89−3.27 | 0.108 | | | |
| > 10mm | 0.76 | 0.27−2.15 | 0.598 | | | |
| AR > 1.6 | 4.89 | 2.76−8.64 | < 0.001 | 5.81 | 3.16−10.70 | < 0.001 |
| SR > 3.0 | 2.40 | 1.34−4.29 | 0.003 | 2.45 | 1.34−4.48 | 0.004 |
| IL-1β, ×10$^2$ | 1.88 | 1.27−2.78 | 0.002 | 1.74 | 1.16−2.60 | 0.007 |
| IL-1ra, ×10$^3$ | 0.67 | 0.56−0.79 | < 0.001 | 0.64 | 0.53−0.77 | < 0.001 |

┼, the parameter was independent risk factor related to rebleeding.

†, the result was adjusted by age, gender, diabetes mellitus, CHD, TIA/ischemic stroke and dyslipidemia.

AR, aspect ratio; SR, size ratio; HR, hazard ratio; CI, confidence interval; CHD, coronary heart disease; TIA, transient ischemic attack.
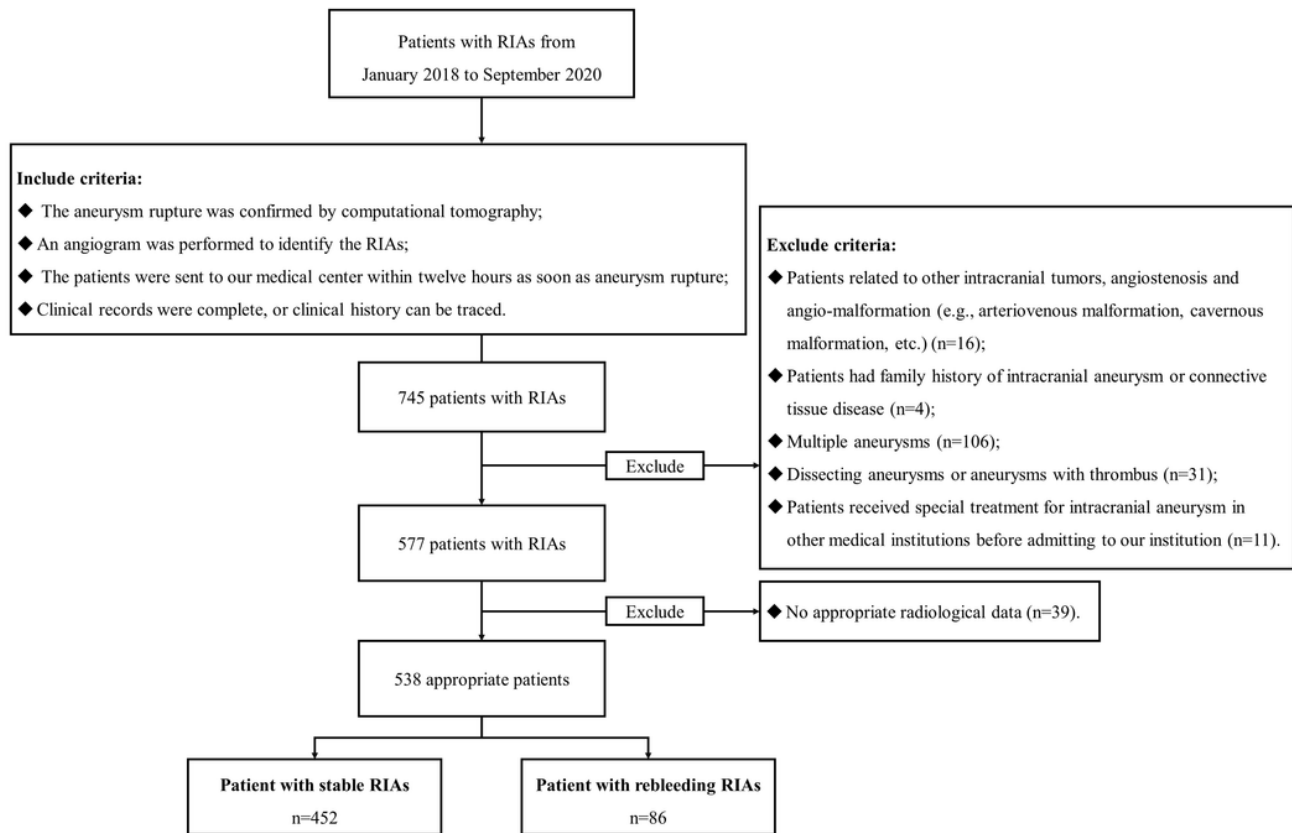
# Figures

**Figure 1**

**The flow chart of patient enrollment.**

This study screened 745 RIA patients and enrolled 538 patients who met the inclusion and exclusion criteria. Of all included 538 patients, 452 patients were diagnosed with stable RIAs and 86 patients had rebleeding RIAs.
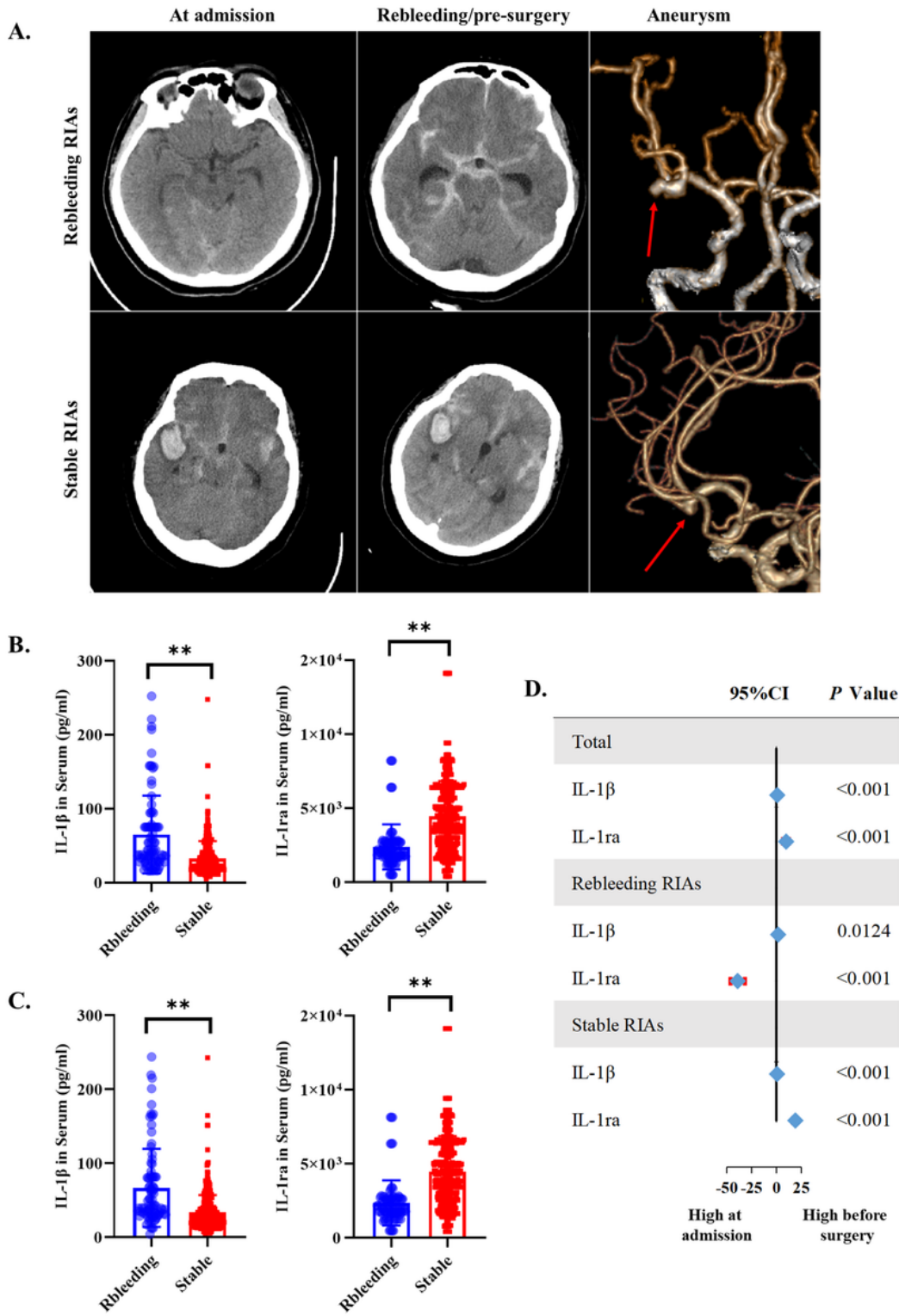
RIAs, ruptured intracranial aneurysms.

**Figure 2**

**Representative cases and IL-1 level before and after rebleeding.**

(A) The CTs and angiograms of two representative cases.

(B) Histograms presenting the serum IL-1β level and serum IL-1ra level between the stable RIAs and rebleeding RIAs on admission.

(C) Histograms presenting the serum IL-1β level and serum IL-1ra level between the stable RIAs and rebleeding RIAs before surgery.

(D) The comparison of serum IL-1β level and serum IL-1ra level before and after rebleeding.

**, $P<0.01$. RIAs, ruptured intracranial aneurysms; CT, computational tomography.



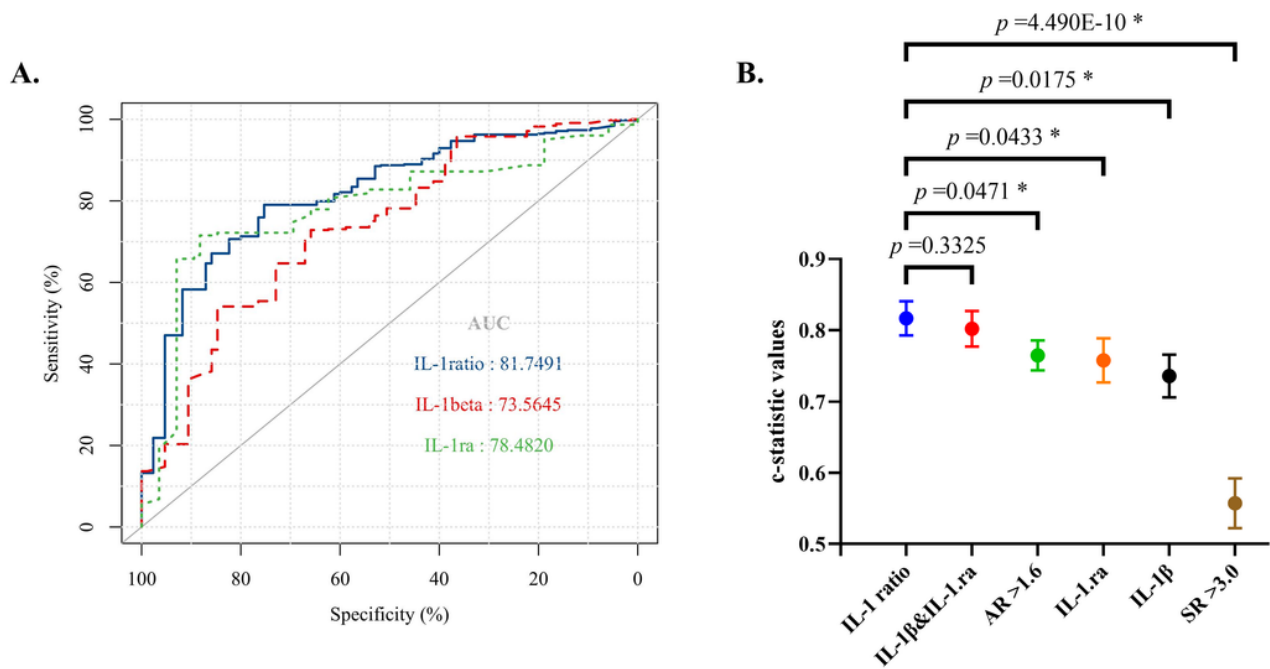Figure 3

The predictive accuracy of IL-1 for the rebleeding after admission.

(A) The c-statistic values of serum IL-1β level, serum IL-1ra level and IL-1 ratio for the rebleeding after admission.

(B) The comparison of the predictive accuracy of each risk factor for the rebleeding after admission.
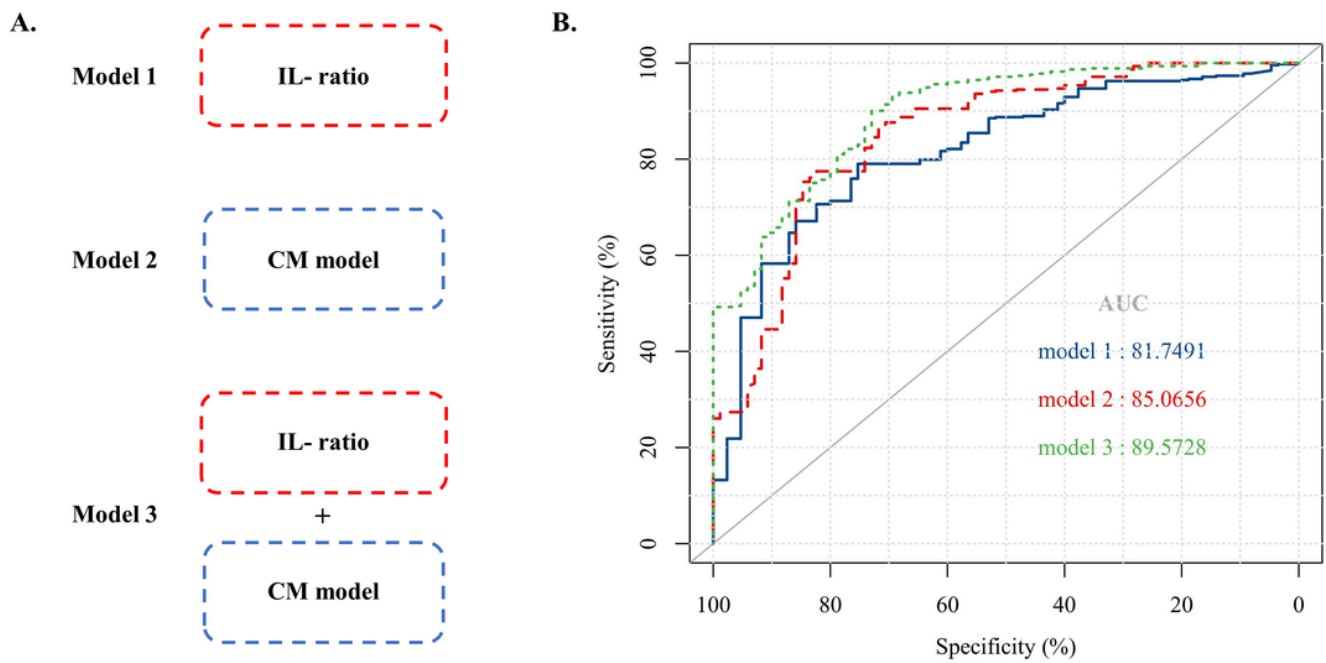
*, $P<0.05$. AR, aspect ratio; SR, size ratio.

**Figure 4**

Evaluation of the value of IL-1 ratio using different models.

(A) Three predictive models were developed in this study. The IL-1 ratio and CM model were combined as model 3.

(B) The c-statistic value of each model for the rebleeding after admission.

*, $P<0.05$. CM model, clinical + morphology model.

**Figures 5, 6 and 7 are not available with this version**

**Figure 5**

These images are not available with this version

# Supplementary Files

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