Association between D-dimer levels and long-term mortality in patients with aneurysmal subarachnoid hemorrhage

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Objective  D-dimer is a marker for hypercoagulability and thrombotic events. The authors sought to investigate whether D-dimer levels predicted long-term mortality in patients with aneurysmal subarachnoid hemorrhage (aSAH).

Methods  This was a retrospective study of patients with aSAH in West China Hospital, Sichuan University, between December 2013 and June 2019. D-dimer levels were measured within 24 hours after admission and were grouped by quartiles. The primary outcome was long-term mortality. Patient deaths were determined through the Household Registration Administration System in China, with a median of 4.4 years of follow-up.

Results  This study included 2056 patients. Compared with patients with the lowest quartile (0.00–0.97 mg/L) of D-dimer levels, the odds of long-term mortality were significantly higher in all other patients, including those with D-dimer levels between 0.97 mg/L and 1.94 mg/L (adjusted hazard ratio [aHR] 1.85, 95% CI 1.32–2.60), those with D-dimer levels between 1.94 mg/L and 4.18 mg/L (aHR 1.94, 95% CI 1.40–2.70), and those patients with the highest quartile (>4.18 mg/L) of D-dimer levels (aHR 2.35, 95% CI 1.70–3.24; p < 0.001). Similar results were observed for the endpoints of 1-year mortality and long-term mortality in 1-year survivors.

Conclusions  Elevated D-dimer levels at admission were associated with short-term and long-term mortality. This biomarker could be considered in future risk nomograms for long-term outcomes and might support future management decisions.


Keywords  intracranial aneurysm; subarachnoid hemorrhage; risk factor; D-dimer

Aneurysmal subarachnoid hemorrhage (aSAH) is a serious disease with a high rate of fatality.1,2 Case fatality after aSAH has decreased by 17% in absolute terms in the past 30 years, and this improvement in short-term survival underscores the need to consider the long-term outcomes.3 Survivors of aSAH still experience a 1.5-fold excess mortality ratio in the long run compared with the general population, mostly related to cardiovascular events.4 The incidence of recurrent aSAH is 15 times that reported in healthy individuals.5 Although secondary prevention of cardiovascular events after clinically proven cardiovascular disease is broadly accepted, the effectiveness of secondary prevention in patients with aSAH has not been established;6 thus, there is a need to develop and validate biomarkers to predict poor long-term outcomes among patients after aSAH.

D-dimer, a product of fibrin degradation, is a marker of thrombin generation and cross-linked fibrin turnover.5,7 D-dimer is an ideal biomarker to predict short-term and long-term cardiovascular events and death in patients with prior vascular disease,7 including venous thromboembolism,8...
could predict mortality, especially in the long term. 15,16 ever, it has been unclear whether D-dimer concentrations be associated with short functional outcomes; 11–14 how -
short studies of patients with aSAH, D-dimer levels have been collected within 24 hours after ad -
mission. D-dimer levels were grouped by quartile with baseline cut points of 0.00–0.97, 0.97–1.94, 1.94–4.18, and > 4.18 mg/L for quartiles 1 (lowest) to 4 (highest), respec-
tively.

Outcome Measures
The primary outcome was long-term mortality (defined as mortality at the longest follow-up). Secondary outcomes were short-term mortality (defined as mortality at 1 year), long-term mortality in 1-year survivors, and in-hospital complications (hydrocephalus, rebleeding, delayed cereral ischemia, seizures, deep venous thrombosis, pulmo-
nary embolism, pneumonia, bloodstream infection, intra-
cranial infection, and urinary tract infection).

Follow-Up
We extracted death records from the database of the Household Registration Administration System with a censoring date of April 1, 2021, with a median of 4.4 years of follow-up and 7.4 years in total. In China, by law, a death certificate should be reported to the household reg-
istration offices within 1 month. Thus, the death certificate database is complete and accurate.

Statistical Analysis
Continuous variables were presented as means (with standard deviations) and compared using analysis of vari-
ance. Categorical variables were reported as counts (fre-
frequencies) and compared using the chi-square test. All tests of significance were 2-sided and p values < 0.05 (2-sided) were considered significant. Multiple imputations were used for continuous variables with missing values, and for categorical variables, all missing variables were coded as other.

We used Kaplan-Meier analysis to examine unadjusted overall survival and the log-rank test to determine sig-
nificant differences between groups. The associations be-
 tween D-dimer levels and mortality were assessed with multivariate Cox regression analysis. Data are presented with the hazard ratio and 95% confidence interval. All variables with a value of p < 0.10 in univariate analysis were selected for inclusion in multivariable analysis.

We conducted a propensity score–matched analysis to minimize bias from confounding variables (age, sex, hy-
pertension, diabetes mellitus, alcohol use, smoking, Fisher grade, Hunt and Hess grade, aneurysm location, aneurysm size, external ventricular drain, and aneurysm treatment) and other important biomarkers (amounts of blood glucose, white blood cells, C-reactive protein, and calcitri-
olin). Propensity score matching of two similar groups was conducted with a 1:1 ratio and a match tolerance of 0.20 SD. This score was calculated using a logistic regression model with D-dimer levels as the outcome and patient fac-
tors as determinants; a difference > 0.1 was considered meaningful. We used survival analysis to compare overall survival, which was performed between matched groups.

All statistical analyses were performed with R version 4.0.3 (The R Foundation for Statistical Computing) and IBM SPSS Statistics version 26 (IBM Corp.).

Results
This cohort study included 2056 patients with aSAH (Supplemental Fig. 1). Baseline characteristics of the pa-
tients, stratified by D-dimer levels, are presented in Table 1. Overall, these patients were more likely to present with larger aneurysms and higher Hunt and Hess and Fisher grades.

In-hospital complications are summarized in Supple-
mental Table 1. First, D-dimer levels were grouped by a median cutoff of 4.18 mg/L. In unadjusted comparisons of D-dimer levels, high D-dimer levels were associated with all reported complications except seizures and pulmonary embolism. After adjustment with multivariate regression analysis, high D-dimer levels, compared with low D-dimer levels, had higher odds for predicting several infectious complications (pneumonia, bloodstream infection, intra-
cranial infection, and urinary tract infection), rebleeding, and deep venous thrombosis. These findings remained robust even in the propensity score–matched analysis.

There was a strong and continuous relationship between D-dimer levels and long-term mortality (HR 3.01, 95% CI
2.49–3.63; Fig. 1) and long-term mortality in 1-year survivors (HR 3.49, 95% CI 2.62–4.65), the values of which were still significant after being adjusted for confounders (aHR 1.55, 95% CI 1.27–1.89 and aHR 1.91, 95% CI 1.42–2.56, respectively). The proportion of patients who died increased according to baseline D-dimer levels.

Kaplan-Meier analysis showed that death during follow-up was more frequent in patients with higher D-dimer levels (p < 0.001; Fig. 2). It also illustrated that patients with D-dimer levels stratified by D-dimer level severity had significantly worse long-term survival except for deaths that occurred within 1 year.

The patients were then categorized into four groups by quartiles of D-dimer levels (Q1–Q4) for outcomes of mortality (Table 2). In univariate analysis, high D-dimer levels were associated with long-term mortality. Multivariable Cox regression analysis identified D-dimer level, age, aneurysm size, Fisher grade, Hunt and Hess grade, external ventricular drain, and aneurysm treatment as independent predictors of long-term mortality (Supplemental Table 2).

Compared with patients with Q1 (lowest) D-dimer levels (0.00–0.97 mg/L), the odds of long-term mortality were significantly higher in patients with Q2 D-dimer levels (0.97–1.94 mg/L) (aHR 1.85, 95% CI 1.32–2.60), in patients with Q3 D-dimer levels (1.94–4.18 mg/L) (aHR 1.94, 95% CI 1.40–2.70), and in patients with Q4 (highest) D-dimer levels (> 4.18 mg/L) (aHR 2.35, 95% CI 1.70–3.24; p < 0.001). In the propensity score–matched analysis, the trend
was still significant \( (p < 0.001) \). Similar trends were evident for 1-year mortality and long-term mortality in 1-year survivors (Supplemental Table 3) in both multivariate Cox regression analysis and propensity score-matched analysis.

We further assessed interactions by variables on D-dimer levels (Fig. 3). Interaction was present regarding the Hunt and Hess grade \( (p = 0.03) \). There was no significant effect modification of the association between D-dimer level and mortality on the basis of age \( (p = 0.47) \), aneurysm size \( (p = 0.28) \), or aneurysm treatment \( (p = 0.26) \).

The area under the curve of the D-dimer for long-term outcome was 0.66 \( (95\% \, \text{CI} \, 0.59–0.72) \), indicating good discriminatory performance. The optimal cutoff value for D-dimer as a predictor for long-term outcome following aSAH was determined as 2.36 mg/L (Supplemental Fig. 2).

**FIG. 1.** Predicted probabilities (red) and observed rates (blue) of long-term mortality in all patients (A) and 1-year survivors (B), with a multivariate model adjusted for age, history of diabetes mellitus, anterior aneurysm location, aneurysm size, Hunt and Hess grade, Fisher grade, external ventricular drain, aneurysm treatment, and concentrations of blood glucose, white blood cells, C-reactive protein, and calcitonin.
Discussion

In this large, single-center cohort study, we found that the D-dimer level at admission was a predictor of mortality after aSAH. More importantly, there appeared to be a dose-response association between elevated D-dimer levels and mortality in patients.

To our knowledge, there are no data available for an association between D-dimer levels and mortality after aSAH. However, we are aware of several small studies, ranging from 3217 to 18712 patients, that have assessed short-term poor functional outcomes among patients with aSAH.12,13,17,18 For instance, Fukuda et al. recently found that high D-dimer levels were associated with poor functional outcomes (OR 1.50, 95% CI 1.15–1.95).12

The findings of our study are consistent with previous studies that showed an association between D-dimer lev-
Elevated D-dimer levels were associated with delayed cerebral infarction; however, these studies did not assess the mechanism of association of D-dimer levels with mortality. This question is interesting because D-dimer levels reflect coagulopathic disturbances. Previous studies found that high D-dimer levels were associated with delayed cerebral infarction; however, these studies did not assess the association between D-dimer levels and rebleeding in patients with aSAH.11,13,17,18 The association of higher D-dimer levels with increased bleeding risk has been shown in other conditions, such as atrial fibrillation, cirrhosis, extracorporeal cardiopulmonary resuscitation, total joint arthroplasty, and acute abdominal aortic dissection.21–27 D-dimer is an indicator of hyperfibrinolysis. Thus, our findings suggested that hyperfibrinolysis may be related to rebleeding after aSAH. In the subgroup analysis, low D-dimer values were associated with long-term mortality in patients with low Hunt and Hess grades (I–III) but not in those with high Hunt and Hess grades (IV–V), with a statistical test for interaction (p = 0.03). While the mechanism is unclear, the subgroup should be interpreted with caution, because spurious positive findings can arise when multiple subgroups are analyzed.28

This study has several notable strengths. The large data set allows adjustment for potential confounders and results in a clear dose-response relationship. Our findings remained significant after the inclusion of most other important biomarkers, including concentrations of blood glucose, C-reactive protein, white blood cells, and calcitonin. In addition, patient deaths were determined according to the household registration database, which has accurate and complete records.

**Limitations**

The study also has several limitations. First, the retrospective study design limited our analyses from which causal inference cannot be derived and which is subject to bias from unmeasured factors. Second, we measured only one biomarker, but other markers might prove to be more useful for risk stratification. Third, we only analyzed all-cause mortality in this study and did not examine the association of D-dimer levels with cause-specific mortality. This question is interesting because D-dimer levels can affect cardiovascular mortality, cancer mortality, and noncardiovascular noncancer mortality, as suggested by a previous study.9 Fourth, we collected data from the electronic medical record, which included the original Fisher grade but not the modified Fisher grade. The modified Fisher grade may predict outcomes more accurately than the original Fisher grade in patients with SAH.29 Finally, the mechanism of association of D-dimer levels with mortality after aSAH has not yet been established. Further studies are needed to definitively delineate how D-dimer levels affect long-term mortality.

**Conclusions**

In patients with aSAH, elevated D-dimer levels at admission were associated with short-term and long-term mortality. This association was consistent, dose-responsive, and present during 7 years of follow-up. This biomarker could be considered in future risk nomograms for long-term outcomes and might support future management decisions.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Jiang. Acquisition of data: Jiang, Fang, P Wang, Yao, X Wang, Zhang, Hai, You. Analysis and interpretation of data: Jiang, Fang, P Wang, Yao, X Wang, Zhang, Hai, You. Drafting the article: Fang, P Wang, Yao, X Wang, Zhang, Hai, You. Reviewed submitted version of manuscript: Jiang, Fang, P Wang, Yao, X Wang, Zhang, Hai, You. Approved the final version of the manuscript on behalf of all authors: Jiang. Statistical analysis: Jiang, Fang, P Wang, Yao, X Wang, Zhang, Hai, You. Administrative/technical/material support: Jiang, Fang, P Wang, Yao, X Wang, Zhang, Hai, You. Online-Only Content

Supplemental Information

Supplemental material is available online.

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