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; 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.6,7 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

ABBREVIATIONS aHR = adjusted hazard ratio; aSAH = aneurysmal subarachnoid hemorrhage.


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* F.F. and P.W. contributed equally to this work.
coronary heart disease, and stroke. In several small cohort studies of patients with aSAH, D-dimer levels have been associated with short functional outcomes; however, it has been unclear whether D-dimer concentrations could predict mortality, especially in the long term.

The aim of this study was to examine the association between D-dimer levels and long-term mortality after aSAH in a large, single-center cohort of patients, whereby long-term data were obtained from a highly accurate and complete death record registration system, the Household Registration Administration System.

**Methods**

**Study Design**

This is a retrospective, single-center, cohort study and was approved by the IRB of West China Hospital. Data were collected from the electronic health records of West China Hospital, Sichuan University, for patients admitted consecutively from December 2013 to June 2019.

**Patient Selection**

This study included patients with aSAH, which was assessed according to neuroimaging, CSF analysis, or intraoperatively by a neurosurgeon. Exclusion criteria included 1) nondefinitive aneurysms, fusiform aneurysms, and aneurysms related to trauma or arteriovenous malformations; aneurysms that were treated before presentation; trauma SAH; and nondefinitive SAH; 2) patients whose household registration was not in Sichuan province or whose personal identification number was not found in the electronic medical record system; and 3) the baseline D-dimer level had not been collected within 24 hours after admission.

**D-Dimer Measurement**

For the purposes of this study, the exposure was the blood concentration of D-dimer. Blood samples were obtained in patients with aSAH within 24 hours after admission. 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), respectively.

**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 cerebral ischemia, seizures, deep venous thrombosis, pulmonary embolism, pneumonia, bloodstream infection, intracranial 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 registra-
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 1.40–2.56), 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

### TABLE 1. Baseline characteristics stratified by baseline D-dimer levels

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>D-Dimer Quartile (mg/L)</th>
<th>p Value for Trend*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.00–0.97 (n = 519)</td>
<td>0.97–1.94 (n = 510)</td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age, yrs (SD)</td>
<td>52.9 (11.9)</td>
<td>54.6 (11.3)</td>
</tr>
<tr>
<td>Female sex</td>
<td>299 (57.6)</td>
<td>340 (66.7)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>132 (25.4)</td>
<td>103 (20.2)</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>133 (25.6)</td>
<td>110 (21.6)</td>
</tr>
<tr>
<td><strong>Medical history</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>112 (21.6)</td>
<td>135 (26.5)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>22 (4.2)</td>
<td>28 (5.5)</td>
</tr>
<tr>
<td><strong>Aneurysm characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior location</td>
<td>394 (75.9)</td>
<td>380 (74.5)</td>
</tr>
<tr>
<td>Mean size, cm (SD)</td>
<td>0.6 (0.5)</td>
<td>0.6 (0.5)</td>
</tr>
<tr>
<td><strong>Hunt &amp; Hess grade</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>53 (10.2)</td>
<td>38 (7.5)</td>
</tr>
<tr>
<td>II</td>
<td>301 (58.0)</td>
<td>275 (53.9)</td>
</tr>
<tr>
<td>III</td>
<td>137 (26.4)</td>
<td>147 (28.8)</td>
</tr>
<tr>
<td>IV</td>
<td>25 (4.8)</td>
<td>42 (8.2)</td>
</tr>
<tr>
<td>V</td>
<td>3 (0.6)</td>
<td>8 (1.6)</td>
</tr>
<tr>
<td><strong>Fisher grade</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>21 (4.8)</td>
<td>24 (5.1)</td>
</tr>
<tr>
<td>2</td>
<td>104 (23.9)</td>
<td>85 (18.0)</td>
</tr>
<tr>
<td>3</td>
<td>116 (26.6)</td>
<td>75 (15.9)</td>
</tr>
<tr>
<td>4</td>
<td>195 (44.7)</td>
<td>287 (60.9)</td>
</tr>
<tr>
<td><strong>External ventricular drain</strong></td>
<td>7 (1.3)</td>
<td>9 (1.8)</td>
</tr>
<tr>
<td><strong>Aneurysm treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clip</td>
<td>326 (62.8)</td>
<td>345 (67.6)</td>
</tr>
<tr>
<td>Coil</td>
<td>58 (11.2)</td>
<td>67 (13.1)</td>
</tr>
<tr>
<td>No treatment</td>
<td>135 (26.0)</td>
<td>98 (19.2)</td>
</tr>
<tr>
<td><strong>Mean baseline biomarker</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>concentrations (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood glucose, mmol/L</td>
<td>7.4 (2.1)</td>
<td>7.8 (2.5)</td>
</tr>
<tr>
<td>White blood cell count, ×10⁹/L</td>
<td>10.5 (3.6)</td>
<td>10.7 (3.6)</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>52.5 (71.9)</td>
<td>59.9 (71.8)</td>
</tr>
<tr>
<td>Calcitonin, pg/ml</td>
<td>0.5 (4.8)</td>
<td>0.6 (4.2)</td>
</tr>
</tbody>
</table>

Values represent the number of patients (%) unless indicated otherwise.
* p values for linear trend for continuous variables are from a generalized linear model, and those for categorical variables are from an ordinal or logistic regression.
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% 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 32 to 187 patients, that have assessed short-term poor functional outcomes among patients with aSAH. 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).

The findings of our study are consistent with previous studies that showed an association between D-dimer lev-
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.

## Acknowledgments

This work was supported by the project of health commission of Sichuan province (19PJ003) (Yu Zhang), the project of Sichuan Science and Technology Bureau (2020YFS0490, 2021YJ0015) (Yu Zhang, Yan Jiang), and the 1:3:5 projects for disciplines of excellence-Clinical Research Incubation Project, West China Hospital, Sichuan University (21HXFH046) (Fang Fang).

### 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. 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. 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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FIG. 3. Subgroup analysis of the association between D-dimer levels and long-term mortality 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.

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

Supplemental Information
Online-Only Content
Supplemental material is available online.

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