Prognostic Value of Serum C-Reactive Protein in Spontaneous Intracerebral Hemorrhage: When Should We Take the Sample?

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Background: Several studies showed a correlation between C-reactive protein and mortality in spontaneous intracerebral hemorrhage. However, the best time to measure C-reactive protein to assess prognosis is not yet clear. The purpose of this study was to determine if initial or H24-C-reactive protein is independently associated with 30-day mortality in intracerebral hemorrhage. *Methods:* This is a retrospective study done within years 2010-2015. All intracerebral hemorrhage cases with missing data or with autoimmune disease or neoplasm were excluded. Univariate and multivariate analyses were assessed for initial C-reactive protein, H24-C-reactive protein, and confounding factors. *Results:* Of 122 patients, 91 were selected. Only H24-C-reactive protein, hematoma volume, and infratentorial origin were independently associated with 30-day mortality in intracerebral hemorrhage. When adjusted with intracerebral hemorrhage score, H24-C-reactive protein with a cutoff value of 30 mg/L independently predicted 30-day mortality. *Conclusions:* This study suggests that H24-C-reactive protein may be a more reliable marker than initial C-reactive protein in the prediction of mortality in intracerebral hemorrhage. A large multicentric study is necessary to confirm the interest of including H24-C-reactive protein to a modified intracerebral hemorrhage score for the prediction of 30-day mortality.
Key Words: Intracerebral hemorrhage—prognosis—mortality—C-reactive protein—inflammation.

Introduction

The global incidence of intracerebral hemorrhage (ICH) is increasing as a result of population aging. Prognosis of patients with ICH depends on the rapid onset of appropriate management, and prevention of systemic complications and of secondary induced brain injury. Although there have been great advances in intensive care management of ICH, the initial assessment of prognosis and clinical outcome using ICH score remains poor.[1] Recent studies showed a growing interest on the use of inflammatory biomarkers to improve prognosis assessment of ICH.[2-4] This inflammation can be explained by 2 mechanisms: a brain damage process or a response to complications.[5,6] Inflammatory biomarkers can be used as prognosis factors or as factors for evaluating therapeutic efficiency. Several studies showed a correlation between C-reactive protein (CRP) and mortality in ICH. However, the best time to measure CRP to assess prognosis is not yet clear.[7-11] The purpose of our study was to determine if initial or H24-CRP is associated with in-hospital and 30-day mortality after ICH.

Methods

Patients

We selected all patients admitted for ICH from January 2010 to December 2015. The diagnosis of ICH was es-

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tablished by cerebral tomodensitometry. We excluded all patients having autoimmune disease or neoplasm. We also excluded patients with missing ICH score or missing initial and H24-CRP measurements. A missing value analysis that included all variables of the dataset was performed to check whether the response mechanism is missing completely at random. A multiple imputation (5 imputations) using regression method was then performed to confirm the results of this study. The following details were recorded: demographic characteristics, risk factors, initial clinical parameters, and initial biological parameters including CRP, complete blood count with white blood cells count (WBC), creatinine, glycemia, and electrolytes. CRP was estimated using a "non-high-sensitivity" turbidimetric method with a measuring range from 1 to 500 mg/L. We considered blood sample as initial (H0-CRP and H0-WBC) when it was made within 8 hours from arrival to the hospital. We considered blood sample at H24 (H24-CRP and H24-WBC) when it was made at 24 ± 6 hours. All cerebral tomodensitometries were evaluated by a radiologist. The maximum height (d1) of the hematoma was calculated by multiplying the number of slices involved by the slice thickness, the maximum width (d2) and length (d3) of the hematoma were measured, and the ICH volume was calculated using the greatest diameters of the hematoma in the following formula: $\frac{1}{2} \times d1 \times d2 \times d3$.[12] The ICH score (Appendix 1) was initially calculated by the physician in charge.[1] Initial active infection was diagnosed according to clinical judgment of the physician in charge. The major outcomes were in-hospital and 30-day mortality. The patients were assessed secondarily for hospital length of stay and the need for mechanical ventilation. Statistical analysis was performed using SPSS software (SPSS Inc, Chicago, Illinois, United States). Univariate analyses were performed to explore the predictive factors of in-hospital and 30-day mortality. Cutoff values for predicting mortality were calculated using the best values of sensitivity + specificity for each factor based on the area under the receiver operating characteristic (ROC) curve. Multivariate logistic regression analyses were then performed using all variables that had $P < .05$ on univariate analyses. A second multivariate logistic regression analysis was performed using cutoff values of variables that had $P < .05$ on univariate analyses. Logistic regressions were performed using the Wald backward method. The median values were calculated with 25 and 75 percentiles for skewed distribution variables, and the means were calculated with 95% confidence interval (CI) or standard deviation for normal distribution variables. All data used in this study were anonymous. This study was approved by the local institutional ethics committee.

Results

We admitted 122 patients with ICH in the emergency and intensive care departments between January 2010 and December 2015. We excluded 31 patients with missing values. Twenty-one patients had missing ICH score, 14 patients had missing initial and H24-CRP, and 2 patients had autoimmune disease or neoplasm. The missing value analysis which included all variables of the dataset showed that the response mechanism is missing completely at random ($P = .814$). Finally, 91 cases were selected. Mortality at 30 days from onset was 37%. Nineteen (21%) patients had active infection on admission, 18 had aspiration pneumonias, and 1 had urinary infection. The initial CRP was not correlated with active infection ($P = .424$). H24-CRP was correlated with active infection ($P = .007$).

On univariate analyses, Glasgow Coma Scale (GCS), ICH score, hematoma volume, intraventricular hemorrhage, infratentorial origin, active infection, H0-WBC, H24-WBC, and H24-CRP were significantly associated with 30-day mortality (Table 1).

The cutoff value of GCS with the best sensitivity (.821) and specificity (.735) based on the area under the ROC curve was 12. The odds ratio (OR) [95% CI] of GCS ≥12 was 12.07 [4.31-33.81]. The areas under the ROC curves of H24-CRP and H0-WBC when tested for 30-day mortality were, respectively, .833 [.725-.942] and .749 [.640-.857]. The area under the ROC curve of hematoma volume when tested for 30-day mortality was .768 [.667-.869].

On multivariate analysis, only H24-CRP, ICH volume, and infratentorial origin were independently associated with 30-day mortality. Multiple imputation analysis confirmed these results. The Nagelkerk R square of the model was .783. The adjusted OR of H24-CRP, ICH volume, and infratentorial origin predicting 30-day mortality is shown in Table 2. We found significant positive correlation between H24-CRP and ICH volume ($P < .001$), with a Spearman's correlation coefficient of .464.

The cutoff values, predicting 30-day mortality, of age, GCS, H24-CRP, H0-WBC, and hematoma volume based on the ROC curve analysis are shown in Table 3. In the second multivariate analysis using cutoff values of these variables, H24-CRP, hematoma volume, and infratentorial origin were independently associated with 30-day mortality. The Nagelkerk R square of the model was .688. The regression model and adjusted OR are shown in Table 3. The OR [95% CI] of H24-CRP ≥30 mg/L adjusted for ICH score was 13.25 [2.58-67.99].

We designed a modified ICH score in which we included CRP ≥30 mg/L. In order to find the best number of points that would be assigned to CRP ≥30 mg/L, we performed a multiple ROC analysis of ICH modified scores, with values of CRP points going from 1 to 4. The best value of points assigned to CRP ≥30 mg/L in ICH modified score was 2 points. The area under the ROC curve (area [95% CI]) of modified ICH score (.940 [.890-0.991]) was superior but not statistically significant to the area