C-reactive protein predicts hematoma growth in intracerebral hemorrhage

Cover title[29]: CRP and early hematoma growth

Mario Di Napoli, MD[*†] Adrian R. Parry-Jones, PhD, MRCP[§] Craig J. Smith, MD, MRCP[§] Stephen J. Hopkins, PhD[§] Mark Slevin, PhD, FRCPath[‖⬥] Luca Masotti, MD[•] Veronica Campi, PhD[#] Puneetpal Singh, PhD[o] Francesca Papa, MD[†] Aurel Popa-Wagner, MD, PhD[◊■] Valerica Tudorica, MD[■■] and Daniel Agustin Godoy, MD[‡]

[word counts: 4445]

[*]*Neurological Service, San Camillo de' Lellis General Hospital, Rieti, Italy*
[†]*Neurological Section, SMDN—Center for Cardiovascular Medicine and Cerebrovascular Disease Prevention, Sulmona, L'Aquila, Italy*
[§]*Vascular and Stroke Centre, Clinical Sciences Building, Manchester Academic Health Science Centre, Salford Royal NHS Foundation Trust, Salford, UK*
[‖]*SBCHS, John Dalton Building, Manchester Metropolitan University, Manchester, UK*
[⬥]Institut *Català de Ciències Cardiovasculars Hospital de la Santa Creu i Sant Pau, Pavelló del Convent Sant Antoni Maria Claret, Barcelona, Spain.*
[•]*Internal Medicine, Cecina Hospital, Cecina, Italy*
[#]*Central Laboratory, Sanatorio Pasteur, Catamarca, Argentina*
[o]*Molecular Genetics Laboratory, Department of Human Biology, Punjabi University, Patiala, India*
[■]*Research Center for Microscopic Morphology and Immunology & Chair of Biochemistry, University of Medicine and Pharmacy of Craiova, Romania*
[◊]*Molecular Psychiatry, Dept of Psychiatry, Medical University Rostock, Germany*
[■■]*Department of Neurology, University of Medicine and Pharmacy, Craiova, Romania*
[‡] *Neurocritical Care Unit, Sanatorio Pasteur, and Intensive Care Unit, San Juan Bautista Hospital, Catamarca, Argentina.*

List of tables and figures: Tables: Table 1 to 2; Figures: Figure 1 to 3

Supplemental Data: electronic file name: Supplemental file [Appendix (n=1); e-Tables (n=1); e-Figures (n=1)]

Key words: C-reactive protein, [7] intracerebral hemorrhage, inflammation, [58] prognosis, [112] outcome.

Subject Codes: 13, 43, 62, 63

Corresponding Author:

Dr. Mario Di Napoli, MD
Neurological Section
SMDN—Center for Cardiovascular Medicine and Cerebrovascular Disease Prevention,
Via Trento, 41
67039 - Sulmona, L'Aquila, Italy
Tel.+39.(0)864.52716
Fax. +39.(0)864.52716
e-mail: mariodinapoli@katamail.com

Abstract

Background and Purpose: Early hematoma growth (EHG) occurs in about one third of patients with spontaneous intracerebral hemorrhage (sICH). We investigated the potential of plasma C-reactive protein (CRP) for predicting early hematoma growth (EHG) after acute sICH.

Methods: Plasma CRP was measured within 6h of onset (median 120 min) in 399 patients with primary or anticoagulant-associated sICH and without recent infection. CT brain scans were performed at baseline and repeated within 24h (median 22h). The primary outcome was EHG, defined as absolute growth >12.5 cm^3 or relative growth >33%. Secondary outcomes included early neurological worsening (ENW) using the Glasgow Coma Scale, and 30-day mortality. Multivariate regression analyses were used to evaluate associations of CRP concentration and outcomes. Kaplan-Meier analysis was used for survival.

Results: EHG occurred in 25.8%, ENW in 19.3%, and mortality was 31.8% at 30 days. Thirty-day mortality was significantly higher in patients with ENW [Hazard ratio (HR):3.21, 95% confidence intervals (95%CI): 2.00–5.17; *P*<0.0001] and in patients with EHG (HR:2.13, 95%CI:1.42–3.18; *P*<0.0001, Logrank test). Median CRP was 12 mg/l [interquartile ranges (IQR):10–17] in the EHG group and 7 mg/l (IQR:4–12.1) in those without EHG (*P*<0.0001). In multivariate analyses, plasma CRP>10mg/l independently predicted EHG (OR:4.71, 95%CI:2.75-8.06; *P*<0.0001) and ENW (OR:2.70, 95%CI:1.50-4.84, *P*=0.0009).

Conclusions: CRP>10 mg/l is independently predictive of EHG and ENW, both of which are associated with increased mortality. Inflammation may be important in contributing to EHG and warrants further investigation.

Introduction

Spontaneous intracerebral hemorrhage (sICH) accounts for 10 to 20% of all strokes, with a high rate of mortality and morbidity among survivors of the acute phase.[1] Early hematoma growth (EHG) occurs in about 20-40% of sICH patients and is a major determinant of early deterioration and poor clinical outcome.[2, 3] Improving our knowledge of the mechanisms underlying EHG could reveal a biochemical marker and helping to discover novel therapeutic targets.

Inflammation is a major feature of pathology associated with sICH.[4-7] Increased levels of peripheral inflammatory markers on admission, such as fever, elevated white blood cell count (WBC), interleukin-6 (IL-6) and fibrinogen are associated with worse short term outcomes.[4, 5, 7] C-reactive protein (CRP) is an acute-phase reactant induced by IL-6 and is associated with worse outcomes at 1-3 months,[15-17] but the relationship between CRP and EHG and short-term outcome is unknown. The aim of this prospective, multicentre study was to assess the sensitivity, specificity, and predictive value of CRP for predicting EHG, early neurological worsening (ENW) and mortality after sICH.

Patients and Methods

We included patients recruited to a prospective, international, multicenter, observational, collaborative registry between January 1, 2009 and December 31, 2011 (**Supplemental file Appendix**).[8, 9] Patients aged ≥18 years presenting with a primary or anticoagulant-associated sICH [defined as sudden intraparenchymal bleeding, confirmed by CT scan, in absence of secondary causes (e.g. brain tumors, vascular malformation, trauma)] were eligible for entry. All patients had baseline clinical data recorded, including demographics, risk factors, co-morbidities, examination findings, Glasgow Coma Scale (GCS) after resuscitation, Hemphill's ICH (oICH) score,[10] routine laboratory panels, and CT scan findings. Data are regularly uploaded from participating centers to a central database, maintained by the statistical center (Sulmona, Italy).

In the present analysis, we included patients that had presented within six hours of onset, with plasma CRP assay at study entry and complete clinical and imaging data. Patients with a history of acute or chronic infection(s) in the four weeks before sICH, clinical evidence of acute infection at admission, other concurrent co-morbidities associated with CRP increase, or where surgery was performed before follow-up CT, were excluded to avoid confounding influences (**Figure e1**). The CRP

analysis was performed locally using high-sensitivity immunoturbidimetric assays, with similar performance characteristics, as previously reported.[11]

Standard clinical care was based on the guidelines of the Stroke Council of the American Heart Association[12] and European Stroke Initiative.[13] Informed consent was obtained from all participants or legal representatives and the protocol was approved by local Institutional Review Boards.
The initial non-contrast CT scan was reviewed to indentify sICH location (basal ganglia, thalamic, lobar, pontine, cerebellar, or other), hematoma volume (ABC/2 method), midline shift (>10 mm by measuring the displacement of the septum pellucidum from the midline), and intraventricular extension (IVH; graded by Graeb score).[14] All patients underwent a second CT scan at 24 hours, or earlier if clinically indicated**.** CT scans were analyzed blinded to clinical information to prevent bias. The interobserver reliability of the ABC/2 method and Graeb score were evaluated by comparing measures in a random sample of 19 scans by local investigators and an independent observer (AP-J).

The primary outcome was EHG, defined as an absolute growth >12.5 cm^3 or relative growth >33% between the initial and follow-up CT.[3, 15, 16] The primary analysis was the relationship between EHG and CRP. Secondary outcomes included ENW and 30-day mortality. ENW was defined as ≥3 point decrease in the GCS score for non-comatose patients (GCS>8), or ≥2 point decrease for comatose patients (GCS≤8), or the presence of a new neurological deficit, or worsening of previous deficit, or the appearance of clinical signs of brain herniation.[17] The cause of death was determined from available medical records. Functional outcome was assessed using the Glasgow Outcome Scale (GOS), categorized as good (GOS 4-5) or poor (GOS 2-3).

To establish a cut-off point for CRP, centiles obtained at admission and the corresponding rates of EHG and ENW were compared using receiver operator characteristic (ROC) curves. To determine whether initial hematoma size affects the performance of CRP, we compared *c* statistics when adjusted for baseline sICH volume (categorized *a priori* as <30 cm^3, 30-60 cm^3, and >60 cm^3). We calculated sensitivity, specificity, positive (+LR) and negative likelihood ratio (-LR), positive (+PV) and negative (-PV) predictive values. The optimal cutpoint for normal and elevated CRP was determined using Youden's method and was tested in the validation set. The cohort was, randomly divided into a *derivation* and *validation* cohort using a 3:1 ratio for this analysis. Inter-rater reliability between centers for imaging parameters was measured with intraclass correlation coefficients (ICCs) with the use of analysis of variance.[18] We used Fisher's exact test for comparisons of dichotomous or

categorical variables, and *t* test or the Wilcoxon rank sum test for continuous variables. For Pearson correlation coefficients, we logarithmically transformed positively skewed CRP data to obtain a normal distribution. We performed univariate analyses to explore the association between CRP concentration and outcomes. A multivariable model was designed to allow for adjusted estimates of the role of the CRP value in predicting the primary outcome. In this model we considered CRP value as a forced variable. We considered additional variables that showed univariate association with the primary outcome and included them in the final model if they showed evidence of a significant effect (P<0.05), or if there was evidence of confounding on CRP value. We assessed two-way interactions among the variables in the final model only. The Kaplan-Meier technique (Logrank test) was applied to survival analysis. Eleven patients had missing clinical outcomes, and they were censored, since we knew their survival status at the time of hospital discharge. Statistical analyses were undertaken using SPSS 18.0 (IBM SPSS Software).

Results

Two-hundred and fifteen men and 184 women (m/w ratio: 1.16; mean age, 71.6±12.8 years) were included (**Figure e1**). Median delay from sICH onset to blood sampling was 120 minutes [interquartile range (IQR) 90–240 minutes]. Median baseline hematoma volume was 15.5 cm^3 (IQR: 12–41). Interrater assessments revealed excellent reliability for ABC/2 technique (ICC: 0.835) and Graeb score (ICC: 0.966).

Median CRP was 9.0 mg/l (IQR: 4–16 mg/l). The correlation between log CRP and delay from symptom onset to blood sampling was 0.277 (*P*=0.001), which remained unchanged after adjusting for age, sex and sICH severity (r=0.297, *P*=0.001). Fifty-four (13.5%) patients underwent hematoma evacuation. ENW occurred in 77 patients (19.3%), 313 (78.4%) remained neurologically stable and 9 (2.3%) improved within the first 24 hours. EHG occurred in 103 (25.8%), was more frequent in patients with ENW (n=58; 75%) than stable patients (n=45; 14%) and did not occur in patients who had clinically improved (*P*<0.0001). Median time from baseline to follow-up CT was 22 hours (IQR: 12–24) and was lower for ENW patients (13 hours, IQR: 6–24) than stable or improved patients (23 hours, IQR: 14–24; *P*<0.0001). Median time from baseline to follow-up CT was 16 hours (IQR: 8–24) for patients with EHG and 22 (IQR: 14–24) for those without (*P*=0.0021).

At 30 days, 127 (31.8%) patients were dead and 242 (60.7%) were either dead or severely disabled (GOS 2-3). Mortality at 30 days was significantly higher in patients with ENW (n=48/77, 62.3%) than in patients without [n=79/322, 24.5%; Hazard ratio (HR): 3.21, 95%CI: 2.00–5.17; *P*<0.0001, Logrank test] and in patients with EHG (n=52/103, 50.5%) than in patients without (n=75/296, 25.3%; HR: 2.13, 95%CI: 1.42–3.18; *P*<0.0001, Logrank test).

Median CRP was 12 (IQR: 10–17) mg/l in the EHG group and 7 (IQR: 4–12.1) mg/l in the EHG negative group (*P*<0.0001) (**Figure 1**). CRP was also significantly higher (*P*<0.0001) in ENW patients [12 (IQR: 8–19) mg/l] compared to stable or improving patients [7.1 (IQR: 4–13.3) mg/l]. In comparison to those without EHG or ENW, no differences were found between median time from symptom onset to CRP assay (232 *vs.* 241 minutes, *P*=0.1959) and (232 *vs.* 240 minutes, *P*=0.3687), respectively.

ROC curves (**Figure 2)** had an area under the curve (AUC) of 0.656 (95%CI: 0.607–0.702, *P*<0.0001) for EHG and 0.647 (95%CI: 0.598–0.694, *P*<0.0001) for ENW. Discrimination was different across the pre-specified categories of baseline hematoma size (<30 cm^3, 30–60 cm^3, >60 cm^3), being better for small and moderate hematoma volumes than for larger hematomas (**Table e1**). Globally, sensitivity was higher than specificity, while for smaller hematoma volumes, specificity was higher than sensitivity. The derivation cohort identified the best cut-off for absolute growth at >10 mg/l (sensitivity 69%, specificity 60%), which produced sensitivity of 90% and specificity of 72% in the validation cohort.

Since there was no difference in median time from baseline to follow-up CT in either CRP group (*P*=0.525), and CRP>10 mg/l was not more common when samples were taken later (181-360 min from onset; *P*=0.0525), we did not stratify by delay-to-plasma collection or to imaging time. A CRP>10 mg/l was not significantly more common with anticoagulant use, but was associated with a more severe clinical presentation, defined by lower GCS and higher oICH scores, and with higher blood glucose concentration and WBC count at admission (**Table 1**). EHG and ENW were significantly more frequent in the CRP>10 mg/l group than in CRP≤10 mg/l group. Mortality at 30 days was significantly greater in the CRP>10 mg/l group (**Table 1**) and Kaplan-Meier analysis revealed the difference occurred primarily within the first week (**Figure 3**).

Univariate analysis revealed significant associations between both EHG and ENW with anticoagulant use, baseline sICH volume and midline shift (**Table 2**). Conversely, ENW was associated with IVH and a higher WBC count. In univariate analysis, CRP>10 mg/l was significantly associated with EHG and ENW. Multivariable analysis did not significantly reduce the effect size for CRP>10 mg/l for EHG, while the estimate of effect size was more attenuated for ENW. Only GCS score (OR: 0.48, 95%CI: 0.25–0.92, *P*=0.026; one point increase) and midline shift (OR: 1.39 95%CI: 1.16–1.94, *P*=0.0361) remained significantly associated with EHG and ENW, respectively. Age, sex, anticoagulant use, sICH volume, IVH and WBC were not independent predictors of either EHG or ENW.

We also considered a model that included both CRP and baseline sICH volume as predictors of the primary outcome, adjusting for time from onset to assay and the interaction between CRP and baseline sICH volume. In this model, the CRP>10 mg/l cut-off continued to be a predictor of the primary outcome (OR: 2.06; 95%CI: 1.11–3.80, *P*=0.0211) whereas baseline sICH volume was not (OR: 0.56; 95%CI: 0.28–1.12, *P*=0.0991). Evidence of a significant interaction between sICH volume and the CRP>10 mg/l in predicting the primary outcome was greater for larger (>60 cm^3) hematoma (OR: 6.59; 95%CI: 3.91–11.10, *P*<0.0001) than moderate (30-60 cm^3) volumes (OR: 2.09; 95%CI: 1.02–4.28, *P*=0.0426).

Discussion

This study demonstrates that higher plasma CRP within the first few hours of sICH onset was highly predictive of both EHG and ENW. It was also more frequently associated with larger hematoma volume, more severe clinical presentation, the presence of IVH, and death at follow-up.

Several points deserve mention. First, the presenting hematoma volumes in the CRP>10 mg/l patients (median 25 cm^3) were almost double those in the CRP≤10 mg/l patients (median 12.3 cm^3). Because hematoma volume at admission predicts both hematoma expansion and poor clinical outcome,[7, 10] one could hypothesize that CRP is a surrogate marker of hematoma volume. However, CRP remained an independent predictor of EHG when corrected for initial hematoma size. Second, the neuroradiological variables assessed in this study reduced the association between CRP and EHG to some extent, suggesting that other clinical and radiological variables could have a role and modify the degree of reported association. Leukoaraiosis, cerebral microbleeds, or brain atrophy, and

previous stroke lesions were not specifically measured. However, plasma CRP concentration has been shown to be strongly associated with each of these pathologies,[19-22] so CRP could represent a marker of vascular risk and advanced biological ageing. It will therefore be important to test these other imaging markers for their associations with EHG and their interaction with the CRP concentration and validate our findings independently.

These results support our previous finding that higher acute plasma CRP is associated with poor outcome and higher mortality at 30-days.[8, 9] This is consistent with a previous study which demonstrated a significant association between plasma IL-6, the major inducer of CRP, and EHG after ICH.[5] The association between IL-6 and ENW was not reported in that study, but other markers of inflammation, including early fever, high WBC and high fibrinogen did predict neurological decline up to 48h after admission in a different analysis of the same cohort.[7] In another study, IL-6 did not predict longer term outcomes.[4]

EHG is an important therapeutic target in sICH and accurately discriminating between those at high and low risk of EHG allows potential treatments to be targeted towards those most likely to benefit. This strategy is employed in ongoing studies which use the 'spot sign', defined by the identification of one or more foci of contrast enhancement within an acute primary parenchymal hematoma on the source images of a CT angiogram (CTA),[23] to select patients to receive haemostatic therapies. However, in a recent observational study,[23] the association with risk of hematoma expansion was less with the spot sign (adjusted risk ratio: 2.3; 95%CI: 1.6–3.1) than we report here for CRP>10 mg/l (adjusted OR: 4.7; 95%CI: 2.8–8.1). Although a model combining both the spot sign and CRP may improve prediction of EHG, measurement of CRP using point-of-care methods has advantages over a CTA, in that it can be easily implemented with lower cost, caries no risk (unlike the radiation dose and risks of iodinated contrast in CTA), and does not require specific expertise to interpret. Rapid measurement of CRP concentrations, shortly after onset in sICH, may therefore be a more practical means of discriminating between those at high and low risk of EHG.

The mechanisms underlying our observations are not fully understood, but warrant further consideration. Apart from activating microglia and complement C3,[24] CRP can directly cause blood-brain barrier disruption and brain edema formation.[25] Experimental studies demonstrate that an acute local inflammatory response to the hematoma can occur within 1 hour of onset,[26] and a systemic state of inflammation is triggered.[7] It seems likely that plasma CRP reflects evolving pro-

inflammatory processes, induced locally and systemically. This may be a consequence of the acute sICH, although the relatively high concentrations of CRP observed so early after onset of sICH suggest that pre-existing inflammation, perhaps associated with underlying sICH etiology, may also have contributed to the risk of EHG. Peripheral inflammation associated with underlying pre-morbid vascular risk profile such as hypertension, smoking and atherosclerosis, even in the absence of clinically apparent infection, is well-recognized to precede and contribute to acute stroke. The presence of perivascular inflammation has also been identified in cerebral amyloid angiopathy, an important cause of ICH in older patients.[27] Since EHG is not well modeled in animal studies we are largely reliant on further clinical studies to further elucidate the mechanisms linking inflammation with EHG. Given that inflammation may play a role in the etiology of sICH, EHG and secondary brain injury, it may represent an important therapeutic target that warrants further investigation.

There are limitations to this study that should be considered when interpreting the results. Several patients died very early after onset, presumably owing to large hematoma volumes or hematoma growth. Exclusion of such patients might have underestimated EHG and the proportion of those with a high early CRP. Another group of patients received treatments that made determination of hematoma growth impossible, such as early surgical evacuation or off-label use of hemostatic drugs in anticoagulated patients. Finally, we cannot exclude potential clinical care confounders, such as do-not-resuscitate orders, blood pressure and glucose control, or intensive care unit care, which might influence the association between CRP and EHG or ENW. In conclusion, these results suggest that identification of patients at increased risk of EHG can be enhanced by measurement of CRP in the first few hours after symptom onset. This may assist patient care and prognostication and may be useful in selecting patients for trials of haemostatic or anti-inflammatory therapies aimed at preventing EHG and thus improving clinical outcomes.

Sources of funding

This study has been partially supported by UEFISCDI, PN-II-PT-PCCA-2011-3, grant no 80/2012 (AP-W).

Disclosures

None of the authors have any conflicting interests.

References

1. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: A systematic review. *Lancet Neurol*. 2009;8:355-369

2. Davis SM, Broderick J, Hennerici M, Brun NC, Diringer MN, Mayer SA, et al. Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. *Neurology*. 2006;66:1175-1181

3. Dowlatshahi D, Demchuk AM, Flaherty ML, Ali M, Lyden PL, Smith EE. Defining hematoma expansion in intracerebral hemorrhage: Relationship with patient outcomes. *Neurology*. 2011;76:1238-1244

4. Castillo J, Davalos A, Alvarez-Sabin J, Pumar JM, Leira R, Silva Y, et al. Molecular signatures of brain injury after intracerebral hemorrhage. *Neurology*. 2002;58:624-629

5. Silva Y, Leira R, Tejada J, Lainez JM, Castillo J, Davalos A. Molecular signatures of vascular injury are associated with early growth of intracerebral hemorrhage. *Stroke*. 2005;36:86-91

6. Wang KW, Cho CL, Chen HJ, Liang CL, Liliang PC, Tsai YD, et al. Molecular biomarker of inflammatory response is associated with rebleeding in spontaneous intracerebral hemorrhage. *Eur Neurol*. 2011;66:322-327

7. Leira R, Davalos A, Silva Y, Gil-Peralta A, Tejada J, Garcia M, et al. Early neurologic deterioration in intracerebral hemorrhage: Predictors and associated factors. *Neurology*. 2004;63:461-467

8. Di Napoli M, Godoy DA, Campi V, del Valle M, Pinero G, Mirofsky M, et al. C-reactive protein level measurement improves mortality prediction when added to the spontaneous intracerebral hemorrhage score. *Stroke*. 2011;42:1230-1236

9. Di Napoli M, Godoy DA, Campi V, Masotti L, Smith GJ, Parry Jones AJ, et al. C-reactive protein in intracerebral hemorrhage.Time course, tissue localization, and prognosis. *Neurology*. 2012;79:690-699

10. Hemphill JC, 3rd, Bonovich DC, Besmertis L, Manley GT, Johnston SC. The ich score: A simple, reliable grading scale for intracerebral hemorrhage. *Stroke*. 2001;32:891-897

11. Roberts WL, Moulton L, Law TC, Farrow G, Cooper-Anderson M, Savory J, et al. Evaluation of nine automated high-sensitivity c-reactive protein methods: Implications for clinical and epidemiological applications. Part 2. *Clin Chem*. 2001;47:418-425

12. Broderick J, Connolly S, Feldmann E, Hanley D, Kase C, Krieger D, et al. Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update: A guideline from the american heart association/american stroke association stroke council, high blood pressure research council, and the quality of care and outcomes in research interdisciplinary working group. *Circulation*. 2007;116:e391-413

13. Steiner T, Kaste M, Forsting M, Mendelow D, Kwiecinski H, Szikora I, et al. Recommendations for the management of intracranial haemorrhage - part i: Spontaneous intracerebral haemorrhage. The european stroke initiative writing committee and the writing committee for the eusi executive committee. *Cerebrovasc Dis*. 2006;22:294-316

14. Graeb DA, Robertson WD, Lapointe JS, Nugent RA, Harrison PB. Computed tomographic diagnosis of intraventricular hemorrhage. Etiology and prognosis. *Radiology*. 1982;143:91-96

15. Brott T, Broderick J, Kothari R, Barsan W, Tomsick T, Sauerbeck L, et al. Early hemorrhage growth in patients with intracerebral hemorrhage. *Stroke*. 1997;28:1-5

16. Kazui S, Naritomi H, Yamamoto H, Sawada T, Yamaguchi T. Enlargement of spontaneous intracerebral hemorrhage. Incidence and time course. *Stroke*. 1996;27:1783-1787

17. Flemming KD, Wijdicks EF, St Louis EK, Li H. Predicting deterioration in patients with lobar haemorrhages. *J Neurol Neurosurg Psychiatry*. 1999;66:600-605

18. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*. 1986;1:307-310

19. Satizabal CL, Zhu YC, Mazoyer B, Dufouil C, Tzourio C. Circulating il-6 and crp are associated with mri findings in the elderly: The 3c-dijon study. *Neurology*. 2012;78:720-727

20. Hoshi T, Kitagawa K, Yamagami H, Furukado S, Hougaku H, Hori M. Relations of serum high-sensitivity c-reactive protein and interleukin-6 levels with silent brain infarction. *Stroke*. 2005;36:768-772

21. Wright CB, Moon Y, Paik MC, Brown TR, Rabbani L, Yoshita M, et al. Inflammatory biomarkers of vascular risk as correlates of leukoariosis. *Stroke*. 2009;40:3466-3471

22. Miwa K, Tanaka M, Okazaki S, Furukado S, Sakaguchi M, Kitagawa K. Relations of blood inflammatory marker levels with cerebral microbleeds. *Stroke*. 2011;42:3202-3206

23. Demchuk AM, Dowlatshahi D, Rodriguez-Luna D, Molina CA, Blas YS, Dzialowski I, et al. Prediction of haematoma growth and outcome in patients with intracerebral haemorrhage using the ct-angiography spot sign (predict): A prospective observational study. *Lancet Neurol*. 2012;11:307-314

24. Ducruet AF, Zacharia BE, Hickman ZL, Grobelny BT, Yeh ML, Sosunov SA, et al. The complement cascade as a therapeutic target in intracerebral hemorrhage. *Exp Neurol*. 2009;219:398-403

25. Kuhlmann CR, Librizzi L, Closhen D, Pflanzner T, Lessmann V, Pietrzik CU, et al. Mechanisms of c-reactive protein-induced blood-brain barrier disruption. *Stroke*. 2009;40:1458-1466

26. Wang J. Preclinical and clinical research on inflammation after intracerebral hemorrhage. *Prog Neurobiol*. 2010;92:463-477

27. Carrano A, Hoozemans JJ, van der Vies SM, van Horssen J, de Vries HE, Rozemuller AJ. Neuroinflammation and blood-brain barrier changes in capillary amyloid angiopathy. *Neurodegener Dis*. 2012;10:329-331

Figure Legend

Figure 1. **C-reactive protein (CRP) concentration in mg/l at admission according to early neurological worsening (ENW; A) and early hematoma growth (EHG; B).** The median is indicated by a solid line, the 1st to 3rd quartile as a box, and whiskers represent 1.5xIQR from each quartile. The 95% confidence interval from the median is represented by the notch on the box.

Figure 2. Receiver operating characteristic (ROC) curve for early neurological worsening (ENW; A) and early hematoma growth (EHG; B). Dotted lines represent 95% confidence intervals.

Figure 3. Risk of death by C-reactive protein (CRP) concentration at admission. Log-rank test *P*<0.0001. Dot lines represent 95% confidence intervals.

Table 1. Characteristics of sICH Patients by concentration of CRP at Admission.

	CRP≤10 mg/l (n=213)	CRP>10 mg/l (n=186)	P Value
Demographic			
Age years, mean (±SD)	71.5 (12.5)	71.6 (13.9)	0.9862
Male sex, n (%)	123 (57.8)	92 (49.5)	0.0977
Clinical			
Hypertension, n (%)	170 (79.8)	145 (78.0)	0.6502
Diabetes mellitus, n (%)	54 (25.4)	45 (24.2)	0.7892
Hypercholesterolemia, n (%)	57 (26.8)	36 (19.4)	0.1841
Antiplatelet use, n (%)	48 (22.5)	43 (23.1)	0.8899
Anticoagulant use, n (%)	13 (6.1)	20 (10.8)	0.0926
GCS score, median (IQR)	14 (11-15)	12 (8-15)	0.0037
ICH score, median (IQR)	1 (1-2)	2 (1-4)	<0.0001
SBP (mmHg), median (IQR)	170 (145-200)	170 (150-200)	0.4265
DBP (mmHg), median (IQR)	100 (80-110)	100 (80-110)	0.5766
PP (mmHg), median (IQR)	70 (60-90)	78 (60-90)	0.4133
Glucose (mmol/l), median (IQR)	7.0 (6.0-9.4)	7.8 (6.2-10.7)	0.0302
WBC (×10^3 cells/l), median (IQR)	7.7 (4.9-15.7)	8.8 (5.0-19.8)	0.0014
Imaging			
EHG, n (%)	26 (12.2)	77 (41.4)	<0.0001
ICH volume, cm^3 median (IQR)	12.3 (11–33)	25 (12.3-90)	<0.0001
ICH volume, n (%)			<0.0001
- <30 cm^3	154 (72.3)	97 (52.2)	
- 30-60 cm^3	32 (17.2)	32 (17.2)	
- >60 cm^3	22 (10.3)	57 (30.6)	
Midline shift (>10 mm), n (%)	34 (16.0)	65 (35.0)	<0.0001
IVH, n (%)	74 (34.7)	105 (56.5)	<0.0001
Graeb Score, median (IQR)	5 (2-8)	5 (2-8)	0.7497
Graeb Score, n (%)			0.0002
- No Blood (score: 0)	139 (65.3)	80 (43.0)	
- Mild (score: 1-4)	36 (16.9)	51 (27.4)	
- Moderate (score 5-8)	23 (10.8)	34 (18.3)	
- Severe (score 9-12)	15 (7.0)	21 (11.3)	
Outcome			
ENW, n (%)	22 (10.3)	55 (29.6)	<0.0001
30-day mortality, n (%)	40 (18.8)	87(46.8)	<0.0001

GCS indicates Glasgow coma scale; CRP, C-reactive protein at admission; ICH, Hemphill's original ICH score, ICH, spontaneous intracerebral hemorrhage; WBC, white blood cells; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; IVH, intraventricular hemorrhage; IQR, interquartile range, ENW, early neurological worsening; EHG, early hematoma growth.

Table 2. Predictors of the primary and secondary outcomes.

	Odds ratio (95% CI)					
	EHG			ENW		
Univariable (selected variables)	OR	95% CI	P Value	OR	95% CI	P Value
Age years (>80 y)*	1.35	(0.83-2.21)	0.2307	1.32	(0.77-2.28)	0.3097
Male sex	1.34	(0.85-2.09)	0.2074	1.17	(0.71-1.93)	0.3097
Hypertension	1.43	(0.88-2.52)	0.1373	1.18	(0.65-2.14)	0.578
Diabetes mellitus	1.51	(0.87-2.62)	0.1429	1.32	(0.72-2.42)	0.3618
Antiplatelet use	1.04	(0.61-1.77)	0.8935	1.05	(0.58-1.91)	0.8652
VKA use	1.37	(1.18-1.78)	0.009	1.28	(1.13-1.59)	0.0008
GCS score (≥14)*	0.44	(0.25-0.75)	0.0029	0.73	(0.41-1.27)	0.2608
ICH score (≥3)*	1.48	(0.85-2.59)	0.1640	1.86	(1.03-3.37)	0.0387
SBP (≥200 mmHg)*	1.09	(0.62-1.91)	0.7569	1.12	(0.60-2.07)	0.7232
Glucose (≥10.11 mmol/l)*	1.66	(0.62-1.15)	0.1429	1.62	(0.67-1.16)	0.1364
WBC (≥10.3×10^3 cells/l)*	1.38	(0.86-2.28)	0.2125	2.21	(1.30-3.72)	0.0034
ICH volume (≥ 60 cm^3)*	2.39	(1.42-4.02)	0.0011	4.50	(2.60-7.79)	<0.0001
Midline shift (≥10 mm)	1.39	(1.24-1.64)	0.0002	1.23	(1.14-1.41)	<0.0001
IVH	0.64	(0.42-1.04)	0.0739	1.44	(1.27-1.74)	0.0017
Graeb score (≥4)*	1.74	(1.05-2.87)	0.0317	1.53	(0.88-2.67)	0.1313
Time of sampling (<180 min)	1.31	(0.77-2.23)	0.3169	1.09	(0.62-1.94)	0.7572
CRP (>10.0 mg/l)	5.08	(3.07-8.40)	<0.0001	3.65	(2.12-6.27)	<0.0001
Multivariable Model †						
CRP (>10.0 mg/l)	4.71	(2.75-8.06)	<0.0001	2.70	(1.50-4.84)	0.0009

OR indicates odds ratio; EHG, early hematoma growth; ENW, early neurological worsening; CGS, Glasgow coma scale; ICH score, Hemphill's ICH score; SBP, systolic blood pressure; WBC, white blood cell count; sICH, spontaneous intracerebral hemorrhage; IVH, intraventricular hemorrhage; CRP, C-reactive protein; VKA, vitamin K antagonists. *Dichotomized at the population 75th percentile. †Final model adjusted for age, sex, anticoagulant use, GCS score, ICH volume, midline shift, IVH, time of sampling and WBC.

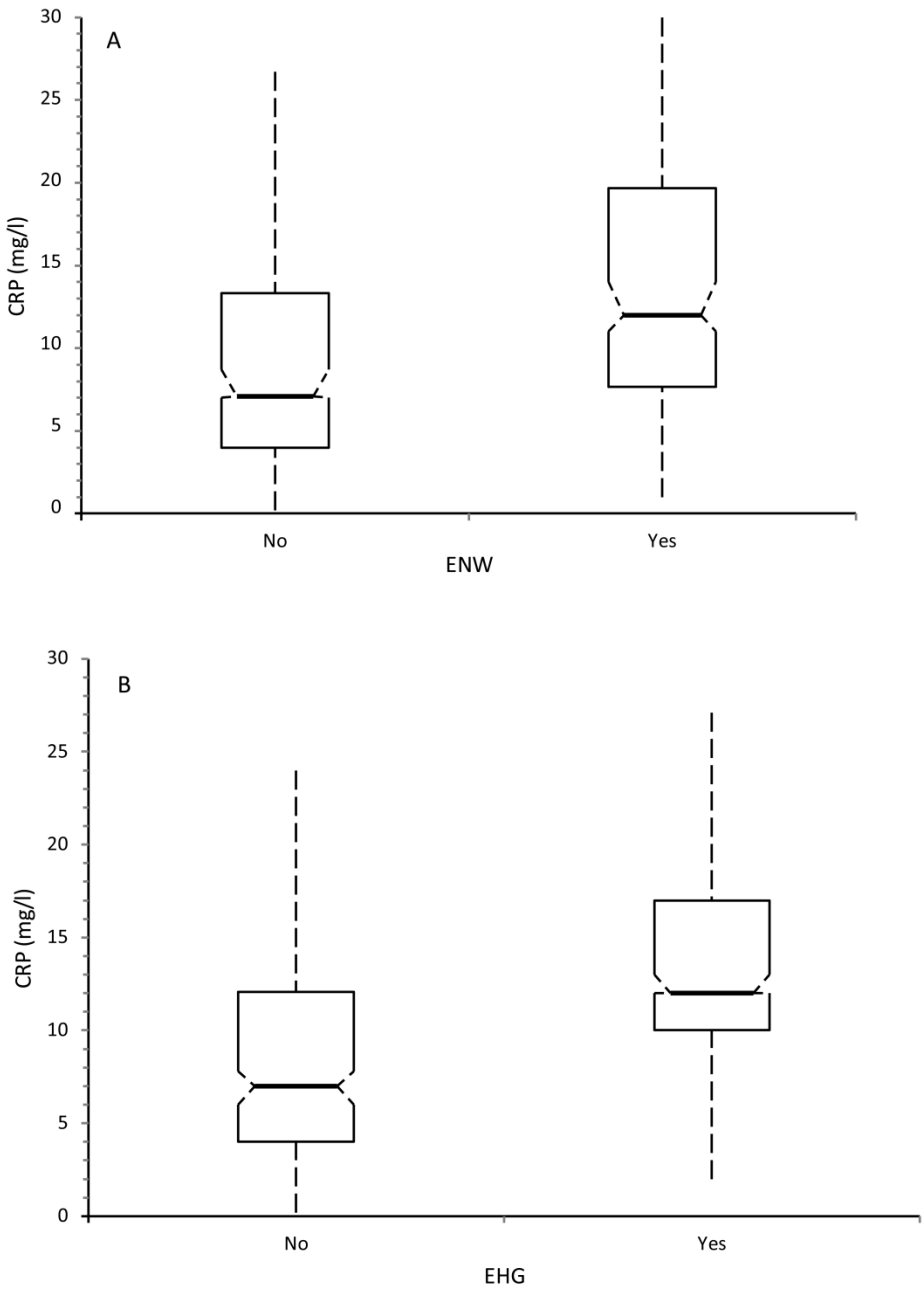

A
30
25
20
15
10
5
0
CRP (mg/l)
No
Yes
ENW
B
30
25
20
15
10
5
0
CRP (mg/l)
No
Yes
EHG

Figure 1

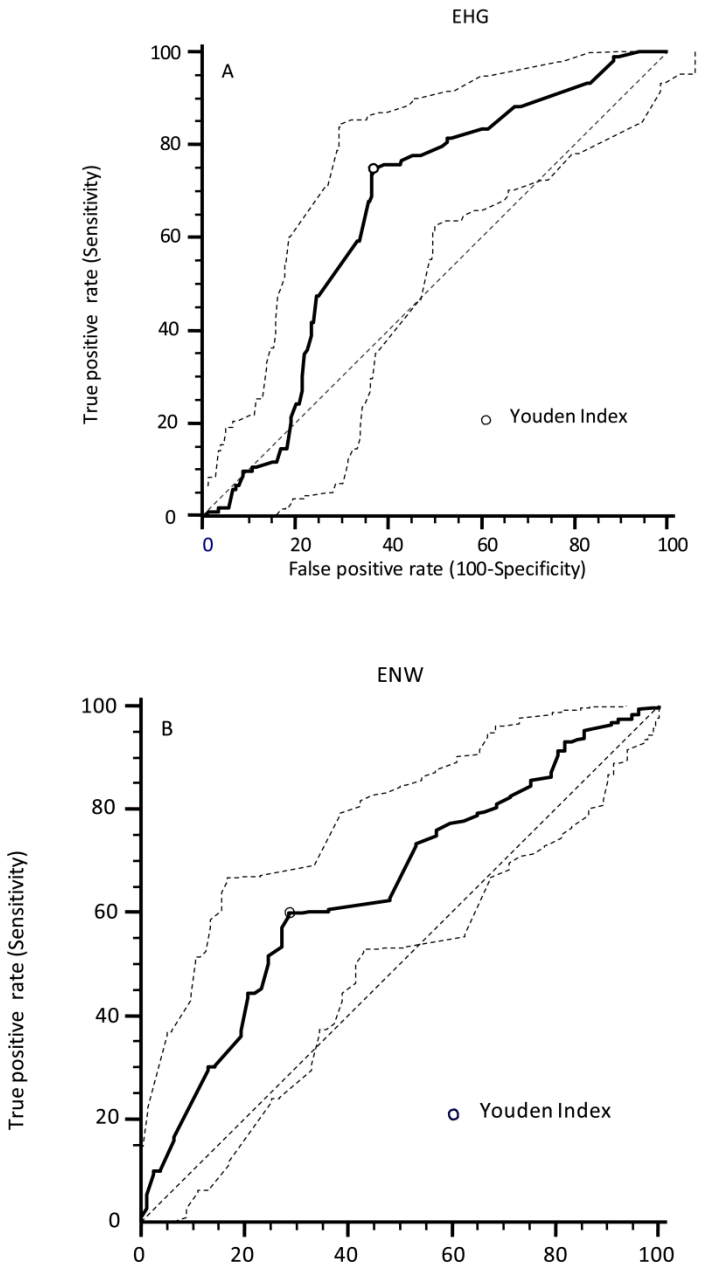
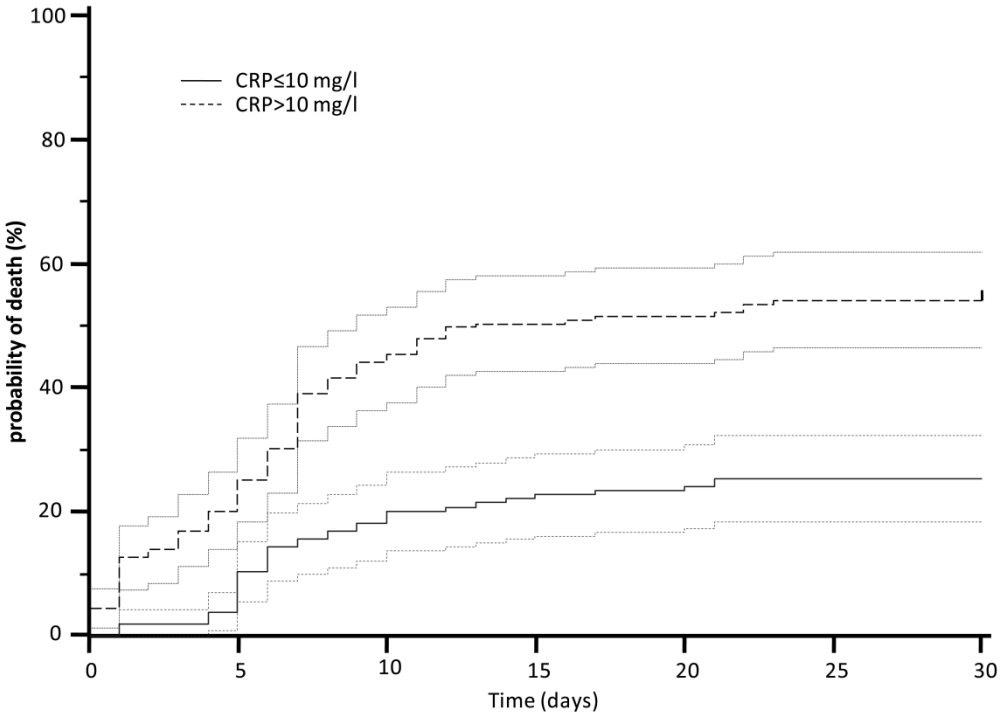

EHG
A
100
80
60
40
20
0
True positive rate (Sensitivity)
Youden Index
0
20
40
60
80
100
False positive rate (100-Specificity)
ENW
B
100
80
60
40
20
0
True positive rate (Sensitivity)
Youden Index
0
20
40
60
80
100

Figure 2



Number at risk							
CRP≤10 mg/l	212	196	181	177	175	173	147
CRP>10 mg/l	179	146	114	106	104	100	89

Figure 3