# Original Contribution

# Leukocyte Count and Intracerebral Hemorrhage Expansion

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***Background and Purpose***—Acute leukocytosis is a well-established response to intracerebral hemorrhage (ICH). Leukocytes, because of their interaction with platelets and coagulation factors, may in turn play a role in hemostasis. We investigated whether admission leukocytosis was associated with reduced bleeding after acute ICH.

***Methods***—Consecutive patients with primary ICH were prospectively collected from 1994 to 2015 and retrospectively analyzed. We included subjects with a follow-up computed tomographic scan available and automated complete white blood cell count performed within 48 hours from onset. Baseline and follow-up hematoma volumes were calculated with semiautomated software, and hematoma expansion was defined as volume increase >30% or 6 mL. The association between white blood cell count and ICH expansion was investigated with multivariate logistic regression.

***Results***—A total of 1302 subjects met eligibility criteria (median age, 75 years; 55.8% men), of whom 207 (15.9%) experienced hematoma expansion. Higher leukocyte count on admission was associated with reduced risk of hematoma expansion (odds ratio for 1000 cells increase, 0.91; 95% confidence interval, 0.86–0.96; *P*=0.001). The risk of hematoma expansion was inversely associated with neutrophil count (odds ratio, 0.90; 95% confidence interval, 0.85–0.96; *P*=0.001) and directly associated with monocyte count (odds ratio, 2.71; 95% confidence interval, 1.08–6.83; *P*=0.034). There was no association between lymphocyte count and ICH expansion (odds ratio, 0.96; 95% confidence interval, 0.79–1.17; *P*=0.718).

***Conclusions***—Higher admission white blood cell count is associated with lower risk of hematoma expansion. This highlights a potential role of the inflammatory response in modulating the coagulation cascade after acute ICH. (***Stroke***. 2016;47:00-00. DOI: 10.1161/STROKEAHA.116.013176.)

**Key Words:** hematoma expansion ■ inflammation ■ intracerebral hemorrhage ■ leukocytes ■ monocytes ■ neutrophils
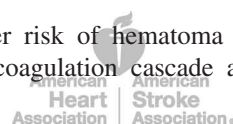
Intracerebral hemorrhage (ICH) is still the deadliest type of stroke and accounts for 10% to 20% of all cerebrovascular events.[1,2] Hematoma expansion occurs in about one third of patients and is strongly associated with poor outcome.[3] As a potentially modifiable determinant of ICH prognosis, hematoma expansion represents an appealing target for acute ICH treatment.[4]

The relationship between acute inflammation, white blood cell (WBC) count and ICH pathophysiology is complex. ICH is associated with leukocytosis, but the inflammatory activation represented by leukocytosis may, in turn, play a role in ICH severity. The results of multiple studies suggest that higher WBC counts accompany more severe ICH as measured by reduced consciousness, higher baseline hematoma volume, and intraventricular hemorrhage presence.[5,6] Leukocyte count has also been associated with higher risk of early neurological deterioration, increased long-term mortality, and poor functional outcome.[7–9] However, Di Napoli et al[10] found that leukocytosis does not independently predict poor ICH prognosis when controlling for other outcome determinants including age, baseline hematoma volume, and admission Glasgow Coma Scale.

Leukocytes interact with platelets, endothelium, and coagulation factors and have been widely recognized as important contributors to facilitating hemostasis in physiological and pathological conditions.[11–13] Acute leukocytosis shifts the hemostatic balance in favor of coagulation and may therefore play an important role in the arrest of bleeding after an ICH occurs. To test the hypothesis that acute leukocytosis limits the extent of bleeding after acute ICH, we investigated whether acute leukocytosis reduced the risk of subsequent hematoma expansion.

# Methods

## Patient Selection

Institutional review board approval was received for all the procedures of this research. Subjects for the present analysis were selected from an ongoing prospectively collected cohort of patients with primary ICH, admitted to our Institution from 1994 to 2015.[14,15] Patients were included if they presented with (1) diagnosis of spontaneous ICH on noncontrast computed tomographic scan (NCCT), obtained within 48 hours from onset, (2) available follow-up NCCT, and (3) complete WBC performed within 48 hours from onset. Exclusion criteria were as follows: (1) evidence of traumatic intracranial bleeding, (2) neoplastic or vascular lesion presumed to be the underlying cause of the hemorrhage, (3) intracranial bleeding secondary to hemorrhagic transformation of ischemic stroke, (4) primary intraventricular hemorrhage, (5) missing clinical and demographic information, and (6) surgical evacuation of the hematoma performed before the follow-up NCCT scan. All the subjects eligible for the study were stratified in quartiles according to the median and interquartile values of WBC count. Admission leukocytosis was defined as total WBC count >11 000 cells/µL.[6]

## Image Acquisition and Analysis

NCCT scans were obtained using an axial technique, with the following acquisition parameters: 120 to 140 kVp, 100 to 500 mA, and 5-mm slice thickness reconstruction. Baseline and follow-up ICH volumes were obtained analyzing NCCT images with a semiautomated computer assisted technique (Analyze Direct 11.0 software). Hematoma expansion was defined as an absolute volume increase >6 mL or a relative volume increase >30% from baseline ICH volume.[16]

## Clinical Variables

Clinical and demographic data were acquired through patient or family members' interviews or with retrospective review of hospital charts. We collected the following information: medical history of hypertension, diabetes mellitus, hypercholesterolemia, antiplatelet therapy, oral anticoagulant treatment. Time from symptom onset to NCCT and WBC blood samples, admission platelet count, activated partial thromboplastin time, and international normalized ratio were also measured.

## Statistical Analyses

Continuous variables were expressed as median (interquartile range) and categorical variables as count (percentage). Differences in continuous variables and categorical variables across WBC quartiles were examined with Kruskal–Wallis test and $\chi^2$ test, respectively. The association between total and differential WBC count and the risk of hematoma expansion was investigated with a multivariable binary logistic regression model, adjusted for previously identified predictors of hematoma expansion[17] and variables with a $P<0.1$ in the univariate analysis comparing WBC quartiles.

Single subjects' predicted probability of hematoma expansion was derived from individual data and from the binary logistic regression model estimates and expressed as a continuous variable ranging from 0 to 1. $P<0.05$ were considered statistically significant, and all the analyses were performed using SPSS version 21, 2012 (www.spss.com).

# Results

After application of the inclusion and exclusion criteria, 1302 patients (median age, 75 years; interquartile range, 64–82; 55.8% men) were included in the analysis (Figure 1). Table 1 shows the demographic and clinical characteristics of the study population. The median WBC count on admission was 9200 cells/µL (interquartile range, 7100–11 700), and 413 (31.7%) patients had admission leukocytosis. A total of 207

patients (15.9%) experienced hematoma expansion. Excluded patients were more likely to have infratentorial hematomas, were more often women and on antiplatelet medications, and were less likely to have a positive medical history of hypertension and hypercholesterolemia ($P<0.05$). In addition, the excluded patients had larger baseline hematoma volume and higher admission WBC count (all $P<0.05$).

Individuals with the highest WBC had higher platelet counts and a trend toward shorter activated partial thromboplastin time. In addition, they had significantly larger baseline hematoma volume and longer time from symptom onset to NCCT and WBC blood sample (Table 2). Hematoma expansion rate was significantly higher in those individuals with the lowest WBC and progressively decreased with increasing WBC quartiles ($P=0.027$).

## Hematoma Expansion Analysis

After adjustment for established predictors of hematoma expansion, higher admission WBC count was independently associated with reduced risk of hematoma expansion (odds ratio for 1000 cells increase, 0.91; 95% confidence interval, 0.86–0.96; $P=0.001$). To determine whether the effect was driven by a particular subset of WBC, we analyzed neutrophil, lymphocyte, and monocyte count separately. Increased neutrophil count was associated with lower risk of hematoma expansion (odds ratio for 1000 cells increase, 0.90; 95% confidence interval, 0.85–0.96; $P=0.001$). Conversely, higher admission monocyte count was an independent predictor of hematoma expansion (odds ratio for 1000 cells increase, 2.71; 95% confidence interval, 1.08–6.83; $P=0.034$). There was no detectable association between lymphocyte count and hematoma expansion (odds ratio for 1000 cells increase, 0.96; 95% confidence interval, 0.79–1.17; $P=0.718$). Table 3 shows the results of the multivariate regression model and all results were unchanged when admission platelet count, activated partial thromboplastin time, time from onset to WBC blood sample, and the presence of intraventricular hemorrhage were also included in the multivariate analysis.

The predicted probability of hematoma expansion was inversely correlated with neutrophil count, and directly correlated with monocyte count, in a linear, dose-dependent relationship (Figure 2).

# Discussion

The different effect of neutrophils and monocytes on hematoma expansion is the most striking result of our study. Higher neutrophil count is associated with reduced risk of hematoma expansion, as opposed to monocyte count that correlates with higher risk.

From a pathophysiological standpoint, our results provide further insights into the complex relationship between acute inflammation and ICH, raising the intriguing hypothesis that the inflammatory response in the hyperacute phase of the disease not only is a nonspecific stress-related reaction but may also be beneficial for ICH patients, improving the coagulation response and limiting hematoma expansion.

Leukocytes interact with platelets, endothelium, and coagulation factors[18] and therefore may play an important role in
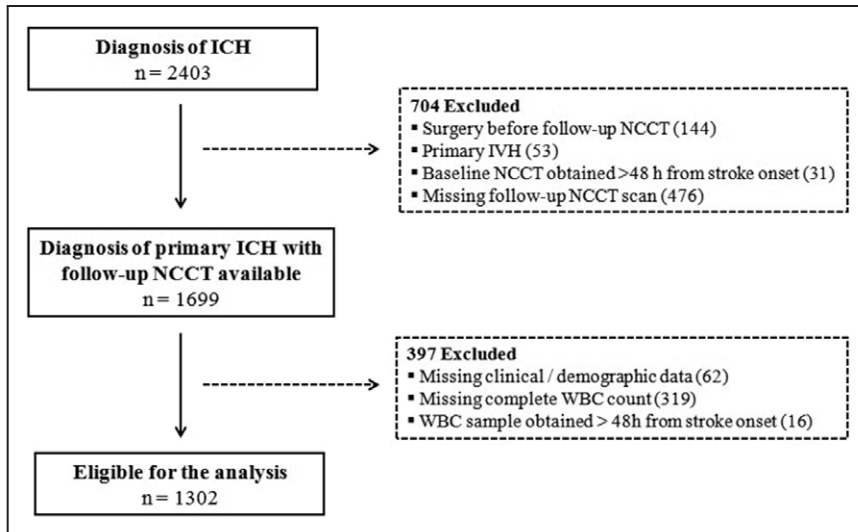
**Figure 1.** Cohort selection process. ICH indicates intracerebral hemorrhage; IVH, intraventricular hemorrhage; NCCT, noncontrast computed tomography; and WBC, white blood cells.

hematoma expansion pathophysiology, through modulation of the coagulation system.[19] This hypothesis is indirectly supported by our observation of a progressively higher platelet count and shorter activated partial thromboplastin time with increasing WBC quartiles.

Neutrophils are the first inflammatory cells to invade the central nervous system when an ICH occurs.[20] Beyond the well-known inflammatory and antimicrobial actions, neutrophils have been increasingly recognized as important contributors to several physiological processes. In particular, activated neutrophils exhibit significant procoagulant properties.[21–23] First, neutrophils shift the coagulation balance in favor of thrombus formation through significant expression and release of tissue factor.[24] Second, neutrophils indirectly increase the amount of active tissue factor downregulating the tissue factor pathway inhibitor.[25] Third, neutrophil extracellular traps can activate platelets, factor X and factor XII, enhance thrombin generation, and contribute to stabilization of the fibrin clot as well.[25–27] Neutrophils' activation in the hyperacute ICH phase may therefore promote a procoagulant state that limits hematoma expansion.

Conversely, the monocyte surface is rich with strong physiological anticoagulants like thrombomodulin and tissue factor pathway inhibitor.[28–30] Therefore, it is biologically plausible that monocyte activation may interfere with clot formation and fibrin stabilization and facilitate further bleeding.

In addition, monocyte activation in animal models and absolute monocyte count in humans were associated with poor outcome after ICH.[31–33] A previous report hypothesized that hematoma expansion may be the link between elevated monocyte count and poor ICH outcome, although this association was not statistically significant.[33] Our results confirm this hypothesis, showing that monocyte count is associated with increased odds of hematoma expansion. Further evidence supporting the association between monocytes and hematoma expansion comes from preclinical data obtained in a mouse model of ICH. Yao et al[34] found that a deficiency of the CCL2-CCR2 monocyte chemoattractant system was associated with

decreased extent of bleeding after intracranial injection of bacterial collagenase.

We observed that subjects with the highest leukocyte count had longer time from onset to baseline NCCT and this may have influenced our analyses because of the known, inverse relationship between time from symptom onset to baseline imaging and the risk of hematoma expansion.[17] However, the association between leukocyte count and the risk of hematoma expansion remained significant after adjusting for time from onset to NCCT in the multivariable regression model.

Neuroinflammation and leukocyte infiltration of the hematoma have been the main targets of several neuroprotective

**Table 1. Baseline Characteristics of the Study Population (n=1302)**

| | |
|---|---|
| Age, median (IQR), y | 75 (64–82) |
| Sex, male, n (%) | 727 (55.8) |
| History of hypertension, n (%) | 1041 (80.0) |
| History of diabetes mellitus, n (%) | 296 (22.6) |
| History of hypercholesterolemia, n (%) | 542 (41.6) |
| Antiplatelet treatment, n (%) | 614 (47.2) |
| Anticoagulant treatment, n (%) | 283 (21.7) |
| Time from symptom onset to NCCT, median (IQR), h | 4.4 (1.9–8.0) |
| Time from onset to blood sample, median (IQR), h | 3.4 (1.6–6.5) |
| WBC count, median (IQR), 1,000 cells/μL | 9.2 (7.1–11.7) |
| Admission leukocytosis, n (%) | 413 (31.7) |
| Baseline ICH volume, median (IQR), mL | 14 (5–34) |
| Presence of IVH, n (%) | 572 (43.9) |
| Hematoma expansion, n (%) | 207 (15.9) |

ICH indicates intracerebral hemorrhage; IQR, interquartile range; IVH, intraventricular hemorrhage; NCCT, noncontrast computed tomography; and WBC, white blood cells.

**Table 2. Comparison of Demographic and Clinical Characteristics Between WBC Quartiles (n=1302)**

| | WBC Quartiles, 1000 Cells/µL | | | | |
|---|---|---|---|---|---|
| | Q1, <7.10 (n = 326) | Q2, 7.10–9.19 (n = 319) | Q3, 9.20–11.70 (n = 328) | Q4, >11.70 (n = 329) | *P* Value |
| Age, median (IQR), y | 75 (65–81) | 75 (65–82) | 76 (65–83) | 74 (62–81) | 0.138 |
| Sex, male, n (%) | 193 (59.2) | 187 (58.6) | 175 (53.4) | 172 (52.3) | 0.171 |
| History of hypertension, n (%) | 256 (78.5) | 249 (78.1) | 267 (81.4) | 269 (81.8) | 0.526 |
| History of diabetes mellitus, n (%) | 83 (25.5) | 65 (20.4) | 66 (20.1) | 82 (24.9) | 0.207 |
| History of hypercholesterolemia, n (%) | 148 (45.4) | 138 (43.3) | 135 (41.2) | 121 (36.8) | 0.140 |
| Antiplatelet treatment, n (%) | 153 (46.9) | 150 (47.0) | 150 (45.7) | 161 (48.9) | 0.875 |
| Anticoagulant treatment, n (%) | 76 (23.3) | 71 (22.3) | 67 (20.4) | 69 (21.0) | 0.808 |
| Time from symptom onset to NCCT, median (IQR), h | 3.1 (1.6–6.8) | 4.0 (1.9–9.9) | 4.6 (1.9–8.4) | 5.1 (3.0–7.9) | 0.002 |
| Time from onset to blood sample, median (IQR), h | 2.4 (1.2–5.0) | 3.9 (1.8–8.3) | 3.5 (2.0–6.5) | 4.1 (2.3–6.5) | <0.001 |
| PLT count, median (IQR), 1000 cells/µL | 197 (154–240) | 221 (178–258) | 230 (191–277) | 255 (209–325) | <0.001 |
| aPTT, median (IQR), s | 26.3 (23.8–30.3) | 26.2 (23.7–29.1) | 26.1 (23.6–29.4) | 25.3 (23.1–29.0) | 0.091 |
| INR, median (IQR) | 1.1 (1.0–1.3) | 1.1 (1.0–1.3) | 1.1 (1.0–1.2) | 1.1 (1.0–1.2) | 0.620 |
| Baseline ICH volume, median (IQR), mL | 10 (4–26) | 11 (4–28) | 16 (6–36) | 22 (7–48) | <0.001 |
| Presence of IVH, n (%) | 122 (37.4) | 113 (35.4) | 152 (46.3) | 185 (56.2) | <0.001 |
| Hematoma expansion, n (%) | 69 (21.2) | 47 (14.7) | 46 (14.0) | 45 (13.7) | 0.027 |

aPTT indicates activated partial thromboplastin time; ICH, intracerebral hemorrhage; INR, international normalized ratio; IQR, interquartile range; IVH, intraventricular hemorrhage; NCCT, noncontrast computed tomography; PLT, platelet; and WBC, white blood cells.

strategies in patients with ICH.[35–37] However, a distinction between acute inflammatory response and chronic inflammation should be made. Although the latter is a proven determinant of secondary damage in ICH,[20,38] acute inflammation and ICH invasion by leukocytes may be beneficial in preventing further hematoma expansion. Furthermore, the divergent effect of neutrophils and monocytes on hematoma expansion highlights the complexity of the acute inflammatory response after an ICH and suggests that future therapeutic strategies should focus on fine modulation of the immune response rather than broad, nonselective anti-inflammatory treatment.

Our results have important implications for future studies and open new areas of investigation in the field of inflammation in ICH. First, to define possible therapeutic targets, further studies are needed to characterize the biological mechanisms underlying the relationships between neutrophils, monocytes, and hematoma expansion. Second, microglia and astrocytes are key players in central nervous system inflammation and little is known about the interaction between peripheral leukocytes and central nervous system immune cells.[31,35] Third, several promising imaging techniques can potentially provide in vivo images of central nervous system inflammation and may improve our understanding of the inflammatory response after ICH.[39]

Finally, from a clinical perspective, hematoma expansion is a potentially modifiable determinant of ICH outcome[3,4] and limiting further bleeding is an appealing therapeutic strategy.[40]

Hematoma expansion occurs in the first hours after an ICH and therefore early identification of patients with the highest risk of expansion is necessary. Current hematoma expansion predictive models are mainly based on clinical and imaging markers.[17,41,42] Neutrophil and monocyte counts are cheap, fast, and widely available biomarkers that might improve our ability to stratify the risk of hematoma expansion in clinical practice.

**Table 3. Multivariable Analysis of Predictors of Hematoma Expansion**

| | OR (95% Wald CI) | *P* Value |
|---|---|---|
| Baseline ICH volume > 30 mL | 4.69 (3.12–7.06) | <0.001 |
| Time from onset to baseline NCCT < 6 h | 5.51 (3.15–9.66) | <0.001 |
| Anticoagulant treatment | 4.40 (2.84–6.82) | <0.001 |
| Total WBC count* | 0.91 (0.86–0.96) | 0.001 |
| Neutrophil count | 0.90 (0.85–0.96) | 0.001 |
| Lymphocyte count | 0.96 (0.79–1.17) | 0.718 |
| Monocyte count | 2.71 (1.08–6.83) | 0.034 |

CI indicates confidence interval; ICH, intracerebral hemorrhage; NCCT, noncontrast computed tomography; OR, odds ratio; and WBC, white blood cells.
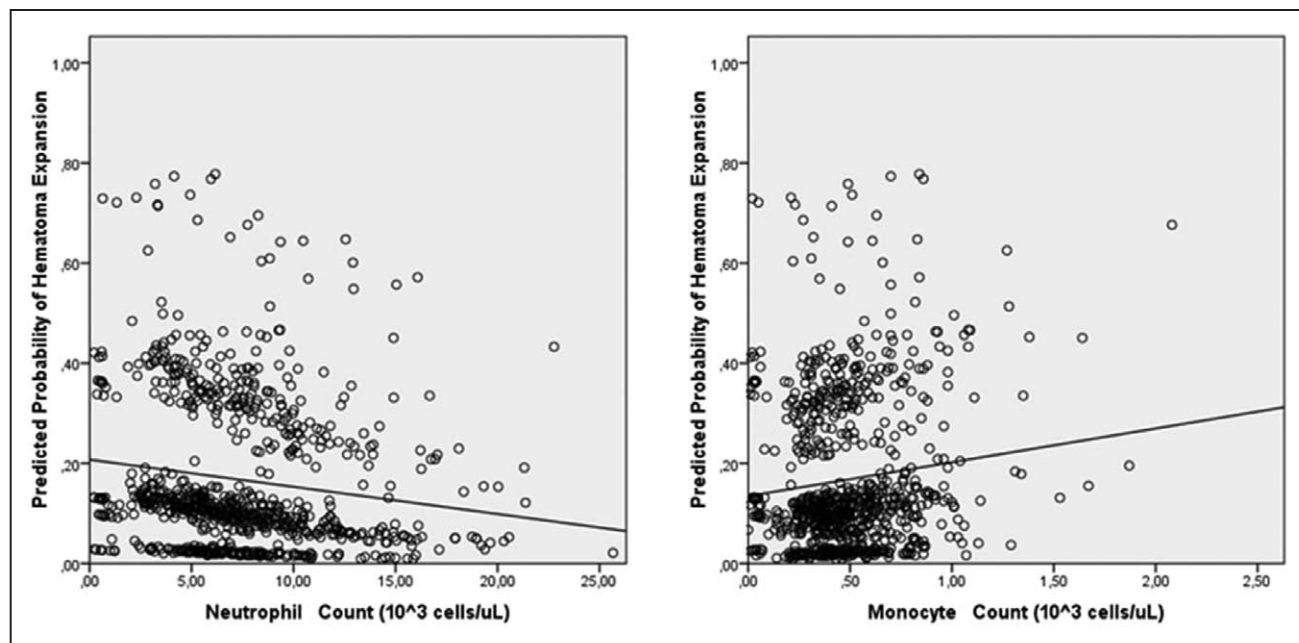*OR for 1000 cells increase.

**Figure 2.** Association between the predicted probability of intracerebral hemorrhage expansion, neutrophil, and monocyte count.

Some limits of this study should be considered. First, our results are derived from a retrospective, single-center analysis. Second, the subjects screened and included were enrolled over a long-time course and changes in ICH management in this period may have influenced our results. Third, a significant proportion of the screened subjects were excluded because of missing follow-up NCCT or missing admission complete WBC count, introducing a potential bias. Finally, although unlikely, the observed elevation in WBC count may be the consequence of chronic inflammatory disorders or acute infections and we were not able to control for these potential confounders in our analysis.

## Conclusion

Monocyte count, as opposed to neutrophil count, is associated with higher risk of hematoma expansion. Our findings highlight the role of inflammation and leukocyte activation in coagulation after acute ICH and may offer an opportunity for early identification and treatment of patients at high risk of hematoma expansion in clinical practice.

## Disclosures

Dr Goldstein received research and consulting fees from CSL Behring and consulting fees from Bristol Myers Squibb. The other authors report no conflicts.

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