Relationship between Baseline White Blood Cell and C-Reactive Protein with Mortality in Patients with Spontaneous Intracerebral Hemorrhage

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Abstract

Background: Inflammation has been shown to play a role in animal models of intracerebral hemorrhage, but actually its role in predicting outcome in spontaneous intracerebral hemorrhage (sICH) is not clear because of the lack of evidence. This study was designed to determine the relationship between baseline white blood cell (WBC) count and clinical outcomes in patients with sICH and to see if WBC count was a significant predictor of outcomes independent of other inflammatory biomarkers such as C-reactive protein (CRP) a well defined prognostic marker in ischemic stroke.

Methods: We evaluated the relationship between baseline WBC count, other baseline variables and biomarkers, neuroradiological findings, and clinical outcomes in 175 consecutive patients with a well-defined diagnosis of sICH admitted into 24 hours in 3 primary referred centers and included in a prospective observational follow-up registry.

Results: Higher baseline wbc counts were associated with hematoma volume at admission (p<0.0001) as well as a greater sich severity (p=0.0016) assessed by glasgow coma scale. a higher baseline wbc count was predictive of higher 30-day mortality, ranging from 10.42% among patients with the lowest wbc count quartile to 66.7 among patients with the highest wbc count quartile (p=0.0001, 2 trend). however, in a multivariable proportional hazards model, wbc count was unable to confirm its predictive prognostic value when adjusted for possible confounding variables and crp concentration quartiles [hazards ratios (hr) 1.23 95% confidence intervals (ci) 0.41-3.68, p=0.7079] while patients with the highest crp concentrations at admission showed a significantly higher risk of 30-day death (hr 2.83, 95%ci 1.14-7.05, p=0.0254) although, crp levels were only lightly associated with stroke severity (p=0.0747).

Conclusions: In patients with sICH, the WBC count was associated with 30-day high mortality rates although, this association reversed when other confounding variables were taken in account suggesting only a role of surrogate biomarker of sICH severity. CRP concentrations appeared more effective in predicting prognosis although its predictive power is limited.

Keywords: Intracerebral hemorrhage; White blood cell; Leukocyte; C-reactive protein; Prognosis

Abbreviations and Acronyms: 95%CI: 95% Confidence Intervals; AMI: Acute Myocardial Infarction; APACHE II: Acute Physiology And Chronic Health Evaluation II; CRP: C-reactive Protein; DIC: Disseminated Intravascular Coagulation; GCS: Glasgow Coma Scale; GOS: Glasgow Outcome Scale; HR: Hazard Ratios; sICH: Hemphill’s ICH Score; sICH: Spontaneous Intracerebral Hemorrhage; WBC: White Blood Cell

Introduction

Spontaneous intracerebral hemorrhage (sICH), defined as spontaneous bleeding into the brain, accounts for 10% to 20% of all strokes [1]. sICH is a devastating clinical event without effective therapies despite progressing in medical knowledge [1-4] with poor outcome[5]. Compared with ischemic stroke and subarachnoid hemorrhage, victims of sICH suffer higher mortality and are left with more severe deficits [3].

Existing contemporary data collected from preclinical and clinical studies indicates that inflammatory processes are involved in sICH [6] and in the progression of sICH-induced brain injury [6,7]. Several prospective studies have been indicated that brain injury secondary to a sICH is characterized by acute local inflammation [7-9] and changes in levels of inflammatory cytokines in body fluids of human patients [10-13]. Elevated levels of inflammatory markers after sICH predict worse prognosis, [14] perihematoma brain edema, [10] early neurological deterioration, [12] and early growth of sICH [11]. Previous clinical studies have provided evidence that supports the role of leukocytes (WBC) in sICH. High WBC count has been reported to be one of the independent predictors of early neurologic

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Received August 23, 2010; Accepted October 21, 2010; Published October 23, 2010

Citation: Godoy DA, Papa F, Campi V, del Valle M, Piñero G, et al. (2010) Relationship between Baseline White Blood Cell and C-Reactive Protein with Mortality in Patients with Spontaneous Intracerebral Hemorrhage. J Neurol Neurophysiol 1:104. doi:10.4172/2155-9562.1000104

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deterioration in sICH [11,12]. Another of the most promising of these inflammatory markers is C-reactive protein (CRP), a biomarker of inflammation that has been shown to predict prognosis in ischemic stroke after adjustment for all major prognostic components [15]. Unfortunately, previous studies have only marginally evaluated CRP as a prognostic marker after sICH with contrasting results [14,16]. This has led to a renewed interest in the study of inflammation markers, including CRP and WBC count, in sICH. Therefore, we evaluated the clinical utility of 2 selected inflammatory markers, WBC and CRP that can be easily determined during the acute phase of sICH as potential outcome predictors in sICH patients.

Materials and Methods

Selection of study population

We prospectively recruited all consenting patients admitted to 3 Intensive Care Units from Buenos Aires State in Argentina, with a diagnosis of sICH within 24 hours after stroke onset, between November 1, 2003 and October 31, 2006. sICH was defined as the sudden and spontaneous intraparenchymal bleeding confirmed by head CT scan with or without intraventricular extension. These primary referred centers have no specific selection criteria for the admission of sICH patients. All participants gave consent directly or through their legal representatives. Our institutional committee approved the study. Admissions fulfilling one or more of the following criteria were excluded: pregnancy (n=2), hemorrhage secondary to brain tumors (n=10), trauma (n=36), hemorrhagic transformation of cerebral infarct (n=4), ruptured aneurysm or vascular malformation (n=27), first evaluation more than 24 hours after symptom onset (n=15), referral from another hospital after diagnosis and initial evaluation (n=13) and missing data due to very early death (n=13). To avoid confounding factors in the determination of inflammatory markers, we also excluded patients with a history of acute or chronic infections ≤4 weeks prior to sICH at admission, concurrent major renal or hepatic disease, cancer, chronic or acute inflammatory diseases, surgery or major trauma in the previous month and those with obvious signs and clinical evidence of acquired in-hospital infection (n=62) (Figure 1). A detailed description of our study methodology has been published previously [17].

Index evaluation

All patients were screened according to a strict protocol consisting of a complete medical history, a full neurological examination, standardized blood tests, at least 1 and usually 2 CT scans of the brain [17]. Surgical criteria were established according to the algorithm of decision in force to authors’ institutions based on the guidelines of Stroke Council of the American Heart Association [2] and European Stroke Initiative recommendations (Appendix I) [18]. The Glasgow Coma Scale (GCS) assessed initial stroke severity and determined after initial evaluation and resuscitation [19], while comorbidities were evaluated according to the Acute Physiology and Chronic Health Evaluation II (APACHE II) score guidelines [20]. sICH Severity was also classified according to original Hembrial’s ICH score (oICH) [21]. The following data were prospectively collected in a computerized database: age, sex, recognized risk factors for sICH (arterial hypertension, alcohol intake, smoking, diabetes mellitus, serum cholesterol levels, anticoagulant treatment), presence of co-morbidities, glucose levels at admission and 72 hours after stroke onset, systolic, diastolic and pulse blood pressure (defined as systolic blood pressure minus diastolic blood pressure), GCS and oICH scores, and CT scan findings. All definitions and diagnostic criteria were previously reported [22,23].

Blood sampling and C-reactive protein assay

All routine biochemistry, hematology and coagulation data were collected at the entry, within 24 hours after sICH onset. Standard techniques were used to measure routine laboratory panels. WBC counts were done with Coulter counter. Blood samples collected in EDTA were also assayed for CRP by use of a high-sensitivity immunoturbidimetric assay (Tina-quant CRP detection method; Roche Diagnostics) performed on a Modular D 914 analysis system (Mannheim, Germany) with a calibrator based upon the international calibration CRM 470. The manufacturer claimed the detection limit to be 0.1 mg/l and the extended measuring range (with reruns) to be 0.1–240 mg/l. The coefficient of variation ranged from 0.6% to 1.3% for the intra-assay precision and from 1.3% to 6% for the inter-assay reproducibility. Baseline WBC counts and CRP concentrations were available in all 175 patients. Laboratory workers were blinded to clinical information and quality control was maintained using standard procedures.

Neuroradiological findings

Investigators who read CT scans were blinded to clinical information and classified neuroradiological findings according to localization (supratentorial or infratentorial), site of sICH (basal ganglia, thalamic, lobar, pontine, or cerebellar), volume of hematoma, midline shift, intraventricular extension of hemorrhage, presence of hydrocephalus and determined in the initial CT scan. sICH hematoma volume was measured with the use of the ABC/2 method, in which A is the greatest diameter on the largest hemorrhage slice, B is the diameter perpendicular to A and C is the approximate number of axial slices with hemorrhage multiplied by the slice thickness [24]. Midline shift was determined by measuring the displacement of the septum pellucidum across midline, using as reference a perpendicular line connecting the anterior and posterior insertions of the falx cerebri at the level of the lateral ventricles and third ventricle [25]. The presence or absence of IVH was also noted on initial head CT and graded according to Graeb scale [26]. Hydrocephalus was determined with the Diringer’s method [27].

Outcome measures and follow-up

The primary end-points, considered in this analysis were 30-day global mortality after sICH and 30-day functional outcome. Global mortality included the combination of any neurological and non-neurological death. Neurological death was defined as death occurring as a direct consequence of the qualifying sICH or of a new bleeding in the absence of other intervening causes. Non-neurological death included all other, vascular and non vascular deaths, not included in the neurological death. Unknown death was diagnosed in the presence of underlying pathology not otherwise specified. 30-day functional outcome was assessed using the Glasgow Outcome Scale (GOS), categorized in good (GOS, 4-5) and worse (GOS, 2-3) functional outcome for statistical assessments [28]. All outcome events were validated by a study physician. For patients in whom 30-day outcome was not available from medical records (n=2), follow-up data were obtained from follow-up visits. We were able to obtain current information on all included patients. All definitions and outcome diagnostic criteria were previously reported and validated by a study physician [17,22,29]. The evaluators were blinded to information regarding inflammation markers that were not used to modify current treatment both during in-hospital and follow-up period.

Statistical analysis

Significance for intergroup differences was assessed by use of the
χ²-test, using Fisher-Freeman-Halton correction when appropriated, by unpaired t-test for continuous normally distributed, and Mann-Whitney U test for non-normally distributed variables. Continuous variables are described as mean±SD or median values with 25th and 75th percentiles, according to manner of distribution. Values for CRP and WBC count were log-transformed as needed for correlation analyses. Correlations between inflammatory marker values and other prognostic factors were also calculated. After examining the distributions, inflammatory marker values were categorized by quartiles for further analyses. Cumulative survival curves were calculated using the Kaplan-Meier method. Cox proportional hazard models were then constructed to estimate hazard ratios and 95% confidence intervals (HR, 95% CI) for the effect of these markers on the independent risk of 30-day mortality. Unadjusted models and models adjusted for demographic characteristics (age and sex), risk factors (arterial hypertension, diabetes mellitus, smoking status and alcohol abuse) and stroke severity (assessed oICH score) were calculated. Interaction terms were included to satisfy assumptions of proportionality, and there was no evidence of overfitting or collinearity. Age (per 10-year increase), oICH scores (per 1-point increase), glucose concentration (per 1.0 mmol/l increase) and sICH hematoma volume (per 1 cc increase) were entered into the Cox proportional hazard models as continuous variables. All the other variables were included as categorical dichotomized variables as previously described [17].

Results

During study period, 357 patients with clinical signs attributable to sICH were identified. After a comprehensive evaluation 175 (103 men and 72 women; m/w ratio: 1.43) patients were included in the present study, the remaining 182 patients (51%) were excluded because they did not fulfill the inclusion criteria for the present study and (Figure 1). Baseline characteristics of patients such as demographic data, risk factor profile, clinical variables and radiological data from baseline CT scans are summarized in (Table 1).

Laboratory findings

Blood samples were drawn with a median time from sICH onset and admission of 120 minutes (25% to 75% interquartile ranges, 55 to 330 minutes). The baseline WBC count ranged from 3.4 to 21.0 x10⁹/l. The mean WBC count was 8.7±3.4 x10⁹/l, the median was 8.0 x10⁹/l, and the 25th and 75th percentiles were 6.5 and 9.9 x10⁹/l, respectively. CRP had a skewed distribution, with median 9.0 mg/l (25% to 75% interquartile ranges, 5 to 17.1 mg/l) and mean 16.0±18.14 mg/l values, respectively. WBC count and CRP were not correlated (r² = 0.01, P=0.1518). WBC was strongly correlated with hematoma volume at admission (r² = 0.33, P<0.0001) and marginally associated with blood glucose (r² = 0.17, P=0.021), but CRP was not. WBC was strongly associated with sICH severity. The proportion of those with WBC count in the highest quartile increased markedly from mild (11.0%, n=11) to moderate (26.8%, n=15) to severe sICH (52.6%, n=10, \( \chi^2 = 21.35, P=0.0016 \)) assessed by GCS. The same results were also obtained using oICH score [5.6% (n=5) vs 34.4% (n=22) vs 40.9% (n=9); \( \chi^2 = 32.98, P<0.0001, \) respectively]. WBC was also associated with history of alcohol abuse, with 17 (35.0%) of non-abusers and 14 (35.0%) of current abusers having WBC count.

![Figure 1: Study flow-chart.](image-url)
in the fourth quartile (P=0.0173). WBC count was not associated with other risk factors. Conversely, CRP levels were only lightly associated with stroke severity (P=0.0747). The proportion of those with CRP levels in the highest quartile among mild stroke patients (25.0%, n=25) did not differ significantly from those with moderate (25.0, n=14) or severe (21.1%, n=4) stroke (P=0.13). Proportions of patients with CRP levels in the highest quartile did not differ by age, sex, and vascular risk factors.

| Causes of death | n (%) |
|-----------------|-------|
| Neurological death | 48 (85.7) |
| Primary injury | 32 |
| Rebleeding | 13 |
| Cerebral edema | 3 |
| Non Neurological | 6 (14.3) |
| ARDS | 1 |
| AMI | 2 |
| DIC | 1 |
| Ventricular arrhythmias | 1 |
| Pulmonary embolism | 2 |
| Cardiac tamponade | 1 |
| Total | 56 |

ARDS indicates Acute Respiratory Distress Syndrome, AMI, Acute Myocardial Infarction, DIC, Disseminated Intravascular Coagulation

Table 2: Causes of death after sICH in 175 patients

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Relationship of WBC count and CRP concentrations to clinical outcomes

30-day mortality rate was 32.2% (n=56), 48 (85.7%) neurological and 8 non-neurological deaths. Causes of death are given in (Table 2). The baseline WBC count was higher in patients who died within 30 days (P<0.0001) but not CRP concentration at admission (P=0.0747) (Table 1). When analyzed as a categorical variable, higher baseline WBC count was predictive of higher 30-day mortality, ranging from 10.4% among patients with the lowest WBC count to 66.7 among patients with the highest WBC count (χ²=31.29, P<0.0001, χ² for trend) (Figure 2A). When stratified by baseline WBC count, event rates diverged over the first 2 weeks (P<0.0001, log-rank test; P<0.0001, χ² for trend) and then remained roughly parallel (Figure 2B). Unadjusted and adjusted HR for the association of WBC and CRP with mortality across quartiles of these markers are presented in (Table 3). The cumulative mortality risk among those in the highest quartile of WBC was 4.21% (95% CI 1.87-9.97%), compared to a risk of 0.24% (95% CI 0.07%-0.67%) among those in the lowest quartile. Cumulative mortality risk among those in the highest quartile of CRP was 1.26% (95% CI 0.58%-2.65%), compared with a risk of 0.54% (95% CI 0.22-1.26%) among those in the lowest quartile. To further explore the relationship between WBC count and CRP concentration with mortality across quartiles we stratified patients according to sICH volume. sICH volume was categorized using previously established cutoffs (<25 cc, 25 to 50 cc, 51 to 80 cc, >80 cc) correlated with outcome (Table 4) [30]. In patients with hematoma volume lower than 25 cc and above 80 cc, WBC count at the entry showed a stronger significantly association with mortality rate than CRP concentration; conversely, in patients with hematoma volume between 25 to 50 cc and between 50 to 80 cc, higher CRP concentration was associated with a higher 30-day mortality rate but not WBC count.

We also examined the relationship between WBC count and surgery, a decision at the discretion of the treating physician. The 30-day mortality rates across the WBC count categories were 9.5%, 13.3%, 34.1% and 65.0% among patients who were not operated (P<0.0001) and 16.7%, 40%, 57.1% and 68.7% among patients who were operated (P=0.1424).

As an elevated WBC count may be a marker of inflammation similar to CRP, we further explored the relationship among WBC count, CRP and clinical outcomes. Patients were stratified by baseline CRP level using a previously established cutoff of 15 mg/l (Table 5) [22]. Among the 130 patients (74.3%) who had a CRP level ≤15 mg/l, WBC count remained a predictor of 30-day mortality. Patients with the lowest WBC count had a 30-day mortality of about 6%, whereas patients with higher WBC count had a 30-day mortality of 26% to 68% (P<0.0001). Among the 45 patients (25.7%) who had an elevated CRP level (>15 mg/l), 30-day mortality was relatively high (23% to 64%) and WBC count remained a predictor of 30-day mortality (P=0.0076). Therefore, patients were categorized into three groups according to their combined WBC and CRP status: 1) low WBC count (lower quartile, <6.5 x10⁹/l) plus low CRP level (<15 mg/l); 2) high WBC count (>6.5 x10⁹/l) plus low CRP level and 3) any WBC count plus high CRP level (>15 mg/l). Using these two markers allowed us to risk stratify patients across an approximate sevenfold graded increase in 30-day mortality (Figure 3). Patients with both a low WBC count plus a low CRP level (n=35) had a low mortality rate (5.7%), patients with an elevated WBC count but a low CRP level (n=95) and patients with any WBC count plus high CRP level (>15 mg/l) (n=45) had a higher mortality rate (63.8% and 60.7%, respectively; P=0.0045, χ² for trend).

In multivariable model after fully adjusting for demographics, risk factors, stroke severity and both inflammatory markers, those in the highest quartile of CRP, had more than twice the risk of death (adjusted HR 2.83, 95% CI 1.14-7.05; P=0.0254), while those in the highest WBC quartile were not more at increased mortality risk (adjusted HR 1.23, 95% CI 0.41-3.68; P=0.7079). sICH score alone (adjusted HR per point increase 3.14, 95% CI 2.29-4.32, P<0.0001) also predicted mortality.
The same analyses were conducted to predict the better 30-day functional outcome. Both WBC count and CRP concentration at admission showed not evident predictive effects on 30-day functional outcome. Only oICH score remained an independent predictor of 30-day mortality from any causes after sICH, stratified by quartile of each marker.

Discussion

The role of inflammation in the physiopathology of sICH is becoming increasingly well recognized [7]. Previous clinical studies have provided evidence that supports the role of leukocytes in sICH. An elevated WBC count was associated with hematoma size [31,32]. Predicted early neurologic deterioration, worse outcome and mortality after sICH [12,14,30,31].

The present study offers several important insights. An inflammatory response is often found at the site of intracerebral hematoma in both human and animal ICH models [33-35]. There is some evidence to suggest that inflammation and the WBC itself

Table 3: Unadjusted and adjusted hazard ratios (HR) for the association between WBC count and CRP concentration at admission with 30-day mortality from any causes after sICH, stratified by quartile of each marker.

Table 4: ICH volume and 30-day mortality stratified by WBC count and CRP concentration quartiles

Table 5: WBC Count, CRP, and 30-day Mortality.
may directly contribute to sICH injury [7]. Leukocytes can promote inflammatory tissue injury indirectly by stimulating macrophages to release pro-inflammatory mediators [36] and via the effects of oxygen-free radicals and complement activation [9]. Our data support these potential pathobiologic processes, as patients with higher WBC counts had greater hematoma volume at admission. Thus, WBC count may be both a marker of a heightened inflammatory state and a direct contributor to hematoma growth and brain injury in the setting of sICH.

In the present study, we observed strong relationships among baseline inflammatory markers (WBC count and CRP concentration) and mortality. These observations are in agreement not only with previous studies of WBC count [12,14,31,32]. But also with studies of other inflammatory markers [9,10,13,37]. The basis for this remains unknown, but the early divergence of the cumulative mortality curves suggests that patients with an elevated WBC count have a higher risk of death from the index event. This early hazard may be related to the possibility that the degree of WBC elevation reflects the severity of the sICH. This hypothesis was supported by our data, in which there were strict correlations between WBC count and both hematoma volume at admission and sICH severity. Moreover, after adjustment for possible confounding factors the association between WBC count and outcome was greatly attenuated and not more significant. From this point of view, WBC count represents an early biological marker of sICH severity. An important advantage of the WBC count as a predictor of sICH severity and clinical outcomes is its ubiquity. A WBC count is available in every hospital and as part of the complete blood count, is almost universally assayed in all patients presenting with sICH. The value for the highest quartile of WBC count in our study was >9.9 x10^9/L, which is close to the upper limit of normal for many laboratories. Vascular-specific anti-inflammatory and antileukocyte therapies are developed as an alternative or adjunctive therapeutic approach to sICH, [7] an elevated WBC count may help identify patients who would benefit from these interventions. Furthermore, the attenuated relationship between WBC count and mortality in patients who underwent surgery is intriguing and may be related to the anti-inflammatory effect of removing intracerebral hematoma and hence importance of hematoma evacuation in patients with an elevated WBC count. This hypothesis would need to be prospectively tested in randomized trials with serial measurements of inflammatory markers.

To our knowledge, this is the first study to look at both CRP and WBC counts in sICH patients. CRP concentration at admission was able to demonstrate only a marginal association (P=0.0747) with 30-day mortality, probably due to a very early determination (120 minutes) after sICH onset. The relationship between inflammatory marker status and 30-day mortality became significant after adjustment for potential confounders including age, gender, risk factors, sICH severity and WBC count. It is conceivable that an increased CRP concentration after sICH onset is due to inflammation related to the pathophysiology of intracerebral hematoma growth and might reflect the extent of the hematoma volume and not to a pre-existent subclinical inflammatory status. Experimental data demonstrate that the acute phase response to intracerebral hematoma occurred later when compared to ischemic stroke [38]. IL-6, a proinflammatory cytokine that regulate at the level of transcription CRP concentrations [39], were observed in blood, cerebrospinal fluid, or brain extracts at 1 h after experimental ICH [38]. The limited data available regarding the time course of acute phase responses in humans showed a more delayed response [7,10,11]. This may suggest that only serial CRP measurements after symptom onset might help to identify those patients who are predisposed to an intensive activation of the inflammatory system. We hypothesize that the measurement of CRP concentrations later after sICH onset and not at admission could be the best marker to estimate these individual reactions of the inflammatory system. However, the significant independent association between inflammatory status and outcome may suggest that the inflammatory system reacts more intensely in some patients and may explain the individual differences in inflammatory response to intracerebral hematoma and the independence in regard to sICH volumes in the acute phase. We found that patients with an elevated CRP concentration had a relatively high risk of dying at 30-day (23.1% to 63.6%) that increase progressively across WBC count strata. Furthermore, among patients with a low WBC count, 30-day mortality was related to baseline CRP concentration: patients had a low mortality rate (5.7%) if they had a low CRP concentration and intermediate mortality rates (23.1% to 58.3%) if they had higher CRP levels (Table 5). Thus, the combined use of baseline WBC count and CRP concentration can be used to stratify mortality risk and identify patients with very low versus intermediate 30-day mortality. At the same time, WBC and CRP appears to be suitable to stratify mortality risk in patients with different volume of the hematoma a measure that correlates well with the outcome and is a very useful indicator for surgery, [30] in a different and complementary way. This aspect is very intriguing and deserves further studies.

There are several limitations to the present study. As an observational investigation, it can only identify associations and not causality. We did not collect information on WBC differential, which may be important. The relationship between CRP and prognosis must be considered exploratory.

In conclusion, in patients with sICH, elevations in a simple, widely available blood test, the WBC count, were associated with 30-day high mortality rates although, this association reversed when other confounding variables are taken in account suggesting only a role of surrogate biomarker of sICH severity. CRP concentrations appear more effective in predicting prognosis although at the moment a too early dosing can limit its predictive power. No significant predictive role for both markers was found for 30-day functional outcome. It is plausible that after further analyses CRP concentrations could be used to stratify patients across a gradation of 30-day mortality risk in sICH patients.

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