Red Cell Distribution Width is Associated with 30-day Mortality in Patients with Spontaneous Intracerebral Hemorrhage

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Abstract

Background: Red cell distribution width (RDW) has been associated with mortality and outcome in a wide variety of non-neurological and neurological diseases, namely in myocardial infarction and acute ischemic stroke, and the reason for this is not completely understood. We aimed to investigate RDW as a potential prognostic marker in patients with intracerebral hemorrhage (ICH).

Methods: This is a retrospective study of consecutive patients with acute non-traumatic ICH admitted to a single center during a 4-year period. We reviewed individual clinical records to collect demographic and baseline information, including RDW at admission, 3-month functional status, and incidence of death during follow-up. Baseline computed tomography imaging was reviewed to classify the location of ICH, and to measure ICH volume and perihematomal edema volume. Patients were divided according to quartile distribution of RDW (RDW-Q1-4).

Results: The final study population consisted of 358 patients, median age 71 years (interquartile range [IQR] 60–80), 55% were male, and median Glasgow Coma Scale was 14 (IQR 10–15), with a mean follow-up of 17.6 months. Patients with higher RDW values were older (p = 0.003), more frequently presented with an active malignancy (p = 0.005), atrial fibrillation (p < 0.001), intraventricular hemorrhage (p = 0.048), and were anticoagulated (p < 0.001). Three-month functional independence was similar throughout RDW quartiles. RDW-Q4 was independently associated with increased 30-day mortality (adjusted odds ratio = 3.36, 95%CI = 1.48–7.62, p = 0.004), but not independently associated with increased mortality after 30 days (adjusted hazards ratio = 0.71, 95%CI = 0.29–1.73, p = 0.448).

Conclusions: RDW is a robust and independent predictor of 30-day mortality in non-traumatic ICH patients, and further studies to understand this association are warranted.

Keywords: Intracerebral hemorrhage, Red cell distribution width, Mortality

Introduction

The global incidence of intracerebral hemorrhage (ICH), which is responsible for 10–20% of all acute strokes and associated with significant burden of disease, has increased in the past decades [1]. Mortality after ICH is significantly higher than in other forms of acute stroke, and population-based studies have shown that nearly one-third of patients with spontaneous ICH die during the first month after the event [2]. Up to this date, there are no known disease-modifying treatments;
therefore, very early case-fatality has remained relatively 
unchanged throughout the years [3]. Most of the more 
robust early mortality predictors, such as age, severity 
of neurologic impairment, ICH volume, intraventricular 
hemorrhage, and infratentorial hemorrhage, are not 
modifiable. In the last years a great amount of attention 
has been paid to neuroimaging biomarkers of prognosis 
in ICH regarding prediction of hematoma expansion [4], 
but the identification of serum biomarkers also has the 
potential to clarify pathophysiological mechanisms and 
identify possible therapeutic targets [5]. Red cell distribu-
tion width (RDW) is a component of the complete blood 
count. It represents the coefficient of variation of circu-
lating red blood cell volume distribution, and may reflect 
states of chronic systemic inflammation, poor nutrition, 
and microcirculation impairment [6]. Elevated RDW was 
found to be a prognostic marker in several vascular dis-
eases, namely in acute myocardial infarction [7], symp-
omatic chronic heart failure [8], and ischemic stroke [9]. 
Studies have also found an association between RDW 
and the occurrence of delayed cerebral ischemia and 
poorer prognosis in patients with acute non-traumatic 
subarachnoid hemorrhage [10]. Up to this date, the pro-
gnostic importance of RDW in patients with spontaneous 
ICH is unclear, and we hypothesize that RDW could also 
serve as a mortality predictor after ICH.

Aims
Our aim was to study the prognostic role of RDW in 
patients with acute spontaneous ICH regarding short-
term and long-term survival, and to explore the relation 
of RDW with other well-known predictors of mortality 
after ICH.

Methods
Study Design and Patient Selection
We conducted a retrospective cohort study of all consec-
utive adult patients admitted to a single university hos-
pital with the diagnosis of non-traumatic ICH during a 
4-year period (January 2014–December 2017). Patients 
were initially selected according to International Classi-
fication of Diseases (ICD9 and 10) codes (intracerebral 
hemorrhage; intracranial hemorrhage, unspecified), and 
the clinical records of all patients were reviewed to con-
firm the diagnosis. We excluded patients with traumatic 
intracranial hemorrhage; hemorrhagic transformation of 
a structural parenchymal lesion (such as ischemic stroke 
or tumor); underlying vascular malformation; isolated 
subdural hematoma without trauma; isolated intraven-
tricular hemorrhage; underlying cerebral venous throm-
busis; unavailable Digital Imaging and Communications 
in Medicine files of first computed tomography (CT); 
unavailable RDW at admission. The Ethics for Health 
Committee of Hospital de Braga approved the study pro-
tocol and waived the need for written informed consent 
from individual patients (reference 153/2018).

Data Collection
Individual clinical records were reviewed to collect 
demographic and clinical information at baseline and to 
collect follow-up information, namely functional out-
come at 3 months measured by the modified Rankin 
Scale and occurrence of death. Early infection was 
defined as an infection diagnosed by the treating phy-
sician in the first 48 h after admission, treatment with 
antiobiotics in the first 48 h after admission for presumed 
infection, or aural temperature ≥ 38.0° accompanied by 
clinical manifestations of infection in the first 48 h after 
admission. Isolated fever, isolated increased inflam-
matory markers, and use of antibiotics without clinical 
manifestations of infection were not considered as evi-
dence of infection. Follow-up was conducted as part of 
the usual clinical care in the outpatient clinics of neurol-
ogy and neurosurgery departments. Cranial CT images 
were reviewed to classify ICH location and the presence 
of intraventricular hemorrhage. ICH volume and perihe-
matomal edema volume were measured using the manual 
planimetric method in ITK-SNAP [11], and raters were 
blinded to RDW information. ICH score was calculated 
for each patient [12]. RDW was measured in venous 
blood samples collected before CT, as part of the routine 
care of these patients, using fully automated measure-
ments (Sysmex XE-5000, Sysmex Inc., Kobe, Japan).

Statistical Analysis
The study population was categorized in four groups 
according to RDW quartile distribution (RDW-Q1 = 11.4–12.7%; 
RDW-Q2 = 12.8–13.2%; RDW-Q3 = 13.3–14.0%; RDW-Q4 = 14.1–23.1%). The groups 
were compared using Pearson Chi square, Kruskal–Wal-
is, and ANOVA tests as adequate. Spearman’s correla-
tion was used to analyze the relationship of RDW with 
other continuous variables. Interobserver agreements 
for ICH volume and perihematomal edema volume were 
calculated using the interclass correlation coefficient for 
single measures. Kaplan–Meier curves for survival dur-
ing the first 30 days and survival after 30 days for the 
total population and stratified according to RDW quartile 
were constructed, and differences between RDW quar-
tiles were calculated using the log rank test. After visual 
analyses of the curves, we found a non-proportionality 
of death occurrence in the first 30 days after ICH (higher in 
the first 10 days), but not after 30 days. Therefore, univar-
able and multivariable binary logistic regression anal-
yses for 30-day mortality were carried out to calculate 
ods ratio (OR) and 95% confidence intervals (95%CI)
for the variables of interest. Variables found to be significantly associated with 30-day mortality in the univariable analysis were included in the multivariable model, except for ICH score because of overlapping variables used to calculate the score and colinearity with other variables. Likewise, univariable and multivariable Cox regression analyses were carried out for mortality after 30 days to calculate hazards ratio (HR) and 95% CI. The statistical threshold for significance was set at \( p = 0.05 \). Statistical analysis was performed using SPSS software (version 22, IBM, New York, USA).

**Results**

After identification of 771 records based on ICD codes, 413 patients were excluded (Fig. 1), and the final study population consisted of 358 patients. Comparisons between characteristics of patients with ICH who were excluded and patients who comprised our final study population are presented in Supplementary Table 1. The final study population had a median age of 71 years (interquartile range [IQR] 60–80), 55% were male patients, median Glasgow Coma Scale (GCS) was 14 (IQR 10–15), and the majority presented with deep ICH (54.5%). Sixty-three patients were anticoagulated at the time of the ICH, the majority of them with a vitamin K antagonist (n = 55) and only 8 with a direct oral anticoagulant. Most of the patients underwent CT ≤ 6 h after symptom onset (n = 204, 57.0%), 35 patients underwent CT > 6 h after symptom onset (9.8%), and 119 patients had undetermined time of symptom onset (33.2%). Mean total follow-up was 17.6 months (standard deviation 16.4), consisting of 520 patient/years, and 30-day mortality was 26.1%. Interobserver agreement was excellent both for ICH volume (interclass correlation coefficient = 0.98) and for perihematomal edema volume (interclass correlation coefficient = 0.94).

Characteristics and values of clinical, laboratory, and imaging variables according to RDW quartiles are presented in Table 1. Patients in higher RDW quartiles were older, and more frequently presented with an active malignancy, atrial fibrillation and were anticoagulated. Among ten patients with active malignancy, five patients presented with hematologic malignancies and all of these presented RDW values in the highest quartile. The frequency of acute anticoagulation reversal among patients who were anticoagulated at baseline was similar in the four groups. There was a trend for patients in higher RDW quartiles to present with lower GCS scores (Spearman correlation: RDW/GCS, \( \rho = -0.106, p = 0.047 \)), but ICH and perihematomal edema volumes were similar in the four groups (Spearman correlations: RDW/ICH volume, \( \rho = 0.039, p = 0.460 \); RDW/perihematomal edema volume, \( \rho = 0.055, p = 0.486 \)). There was no difference in ICH location, but patients with higher RDW more frequently presented with intraventricular hemorrhage. The ICH score was higher in patients in higher RDW quartiles (Table 1), and a positive correlation between RDW and ICH score was found (Spearman correlation: RDW/ICH score, \( \rho = 0.135, p = 0.011 \)). Concerning laboratory variables, patients in higher RDW quartiles had lower hemoglobin and lower hematocrit values (Spearman correlations: RDW/hemoglobin, \( \rho = -0.231, p < 0.001 \); RDW/hematocrit \( \rho = -0.148, p = 0.005 \)), and higher C reactive protein values (Spearman correlation: RDW/CRP, \( \rho = 0.218, p < 0.001 \)).

![Patient selection flowchart. DICOM: Digital Imaging and Communications in Medicine. RDW: red cell distribution width](image_url)
Survival curves during the first 30 days after ICH are presented in Fig. 2a, b, and show higher mortality in the groups with higher RDW quartiles (*p* < 0.001). In the univariable logistic regression analysis for 30-day mortality, belonging to RDW-Q4 group was associated with an increased risk of death (OR = 1.60, 95%CI = 1.30–1.97, *p* < 0.001). In the multivariable analysis, the only independent predictors of 30-day mortality were GCS, Table 1 Baseline characterization of patients according to distribution of red cell distribution width in quartiles

|                      | RDW Q1 (n = 94) | RDW Q2 (n = 89) | RDW Q3 (n = 89) | RDW Q4 (n = 86) | p        |
|----------------------|-----------------|-----------------|-----------------|-----------------|----------|
| Age (years)          | 66.5 (57–76)    | 71 (59.5–81)    | 70 (61.5–79.5)  | 75 (65–84)      | 0.003    |
| Male sex             | 55 (58.5)       | 54 (60.7)       | 46 (51.7)       | 43 (50.0)       | 0.411    |
| Previous functional dependency | 14 (14.9)    | 19 (21.3)       | 19 (21.3)       | 19 (22.1)       | 0.577    |
| Previous stroke      | 16 (17.0)       | 18 (20.2)       | 17 (19.1)       | 18 (20.9)       | 0.916    |
| Arterial hypertension| 78 (83.0)       | 73 (82.0)       | 79 (88.8)       | 70 (81.4)       | 0.525    |
| Dyslipidemia         | 48 (51.1)       | 43 (48.3)       | 42 (47.2)       | 43 (50.0)       | 0.955    |
| Diabetes             | 26 (27.7)       | 23 (25.8)       | 19 (21.3)       | 19 (22.1)       | 0.719    |
| Active malignancy    | 0               | 1 (1.1)         | 2 (2.2)         | 7 (8.1)         | 0.005    |
| Atrial fibrillation  | 7 (7.4)         | 9 (10.1)        | 19 (21.3)       | 25 (29.1)       | <0.001   |
| Antiplatelet therapy | 30 (31.9)       | 29 (32.6)       | 22 (24.7)       | 18 (20.9)       | 0.235    |
| Anticoagulation therapy | 8 (8.5)      | 10 (11.2)       | 17 (19.1)       | 28 (32.6)       | <0.001   |
| Glasgow Coma Scale, total | 14 (10–15)    | 13 (10–15)      | 14 (10–15)      | 13 (9–14)       | 0.054    |
| Systolic blood pressure (mmHg) | 160 (141–182)   | 157 (137–180)   | 161 (143–182)   | 156 (133–179)   | 0.620    |
| Diastolic blood pressure (mmHg) | 88 (73–97)     | 82 (70–97)      | 83 (71–100)     | 89 (71–99)      | 0.699    |
| Blood glucose (mg/dL) | 127 (110–178)   | 132 (110–167)   | 125 (106–163)   | 133 (102–174)   | 0.768    |
| Hemoglobin (g/dL)    | 14.2 (12.9–15.1)| 13.6 (12.7–14.6)| 13.6 (12.4–15.0)| 12.8 (11.5–14.1)| <0.001   |
| Hematocrit (%)       | 41.7 (37.5–43.5)| 39.8 (37.2–42.5)| 40.1 (36.6–44.3)| 38.3 (35.1–41.9)| 0.008    |
| Mean corpuscular volume (fl) | 90.7 (87.1–94.1)| 90.0 (86.9–94.2)| 90.8 (86.9–94.7)| 91.1 (86.4–94.3)| 0.942    |
| Platelet count (×10^3/μL) | 200 (± 56)     | 201 (± 55)      | 196 (± 68)      | 185 (± 77)      | 0.374    |
| Neutrophil/lymphocyte count ratio | 3.9 (2.2–8.2) | 3.8 (2.1–6.7) | 4.1 (2.0–7.3) | 3.9 (2.1–7.5) | 0.890    |
| International normalized ratio | 1.0 (1.0–1.1) | 1.0 (1.0–1.1) | 1.1 (1.0–1.3) | 1.1 (1.0–2.1) | <0.001   |
| Activated partial thromboplastin time (s) | 26.8 (24.3–29.0) | 27.4 (25.5–30.4) | 29.0 (25.7–34.0) | 30.8 (25.9–37.7) | 0.001    |
| Prothrombin time (s) | 11.9 (11.4–12.4)| 12.0 (11.6–12.9)| 12.4 (11.6–14.5)| 13.0 (11.7–22.1)| <0.001   |
| C reactive protein (mg/dL) | 2.9 (2.9–5.3)  | 2.9 (2.9–4.6)   | 2.9 (2.9–10.3)  | 4.8 (2.9–12.6)  | 0.001    |
| ICH primary location  |                |                 |                 |                 |          |
| Lobar                | 27 (28.7)       | 28 (31.5)       | 25 (28.1)       | 34 (39.5)       | 0.341    |
| Deep                 | 52 (55.3)       | 49 (55.1)       | 54 (60.7)       | 40 (46.5)       | 0.306    |
| Infratentorial       | 14 (14.9)       | 12 (13.5)       | 12 (13.5)       | 12 (14.0)       | 0.992    |
| Intraventricular hemorrhage | 31 (33.0)     | 34 (38.2)       | 44 (49.4)       | 43 (500)        | 0.048    |
| ICH volume (mL)      | 14.1 (4.8–52.2) | 12.1 (4.7–29.6) | 21.9 (3.9–57.9) | 19.7 (5.5–37.6) | 0.148    |
| Penhemosmal edema volume (mL)| 12.6 (4.5–37.3) | 8.9 (3.5–23.1)  | 15.1 (4.4–34.7) | 16.8 (6.1–41.3) | 0.090    |
| Penhemosmal edema/ICH Ratio | 0.8 (0.6–1.1) | 0.9 (0.5–1.3)   | 0.8 (0.5–1.1)   | 0.8 (0.6–1.2)   | 0.424    |
| Anticoagulation reversal (among anticoagulated patients) | 7 (87.5) | 7 (70.0)       | 14 (82.4)       | 24 (85.7)       | 0.700    |
| Early infection*     | 18 (19.8)       | 23 (27.7)       | 14 (16.9)       | 18 (22.2)       | 0.373    |
| Baseline ICH score   | 1 (1–2)         | 1 (0–2)         | 1 (1–3)         | 2 (1–3)         | 0.030    |
| Functional independence at 3 months† | 26 (28.9) | 24 (27.3)     | 18 (20.7)       | 18 (20.9)       | 0.461    |
| Death at 30 daysΔ   | 12 (12.8)       | 14 (15.7)       | 28 (31.8)       | 39 (45.9)       | <0.001   |

ICH: intracerebral hemorrhage. RDW Q1-4: red cell distribution width quartiles

Data presented as n (%), median (interquartile-range) and mean (± SD). RDW: red cell distribution width. ICH: intracerebral hemorrhage

*Data missing for 20 patients

†Data missing for 7 patients

‡Data missing for 1 patient

Δ Data missing for 2 patients
international normalized ratio, ICH volume, and RDW-Q4 (adjusted OR = 3.36, 95% CI = 1.48–7.62, \( p = 0.004 \)) (Table 2). After exclusion of patients who were anticoagulated, the results of the multivariable analysis did not change significantly (data not shown). Survival curves for the period after 30 days since ICH are presented in Fig. 2c, d, and show a nonsignificant higher mortality in the groups with higher RDW quartiles (\( p = 0.057 \)). In the univariable Cox regression analysis, belonging to RDW-Q4 was associated with an increased risk of death in the
period after 30 days since ICH (HR = 1.86, 95% CI = 1.03–3.38, \( p = 0.041 \)), but in the multivariable analysis, it was no longer a predictor of death after 30 days (adjusted HR = 0.71, 95% CI = 0.29–1.73, \( p = 0.448 \)).

**Discussion**

The major conclusion of our study is that higher RDW values are associated with 30-day mortality in non-traumatic ICH patients, and its predictive role is independent of other well-known factors associated with early mortality, namely Glasgow Coma Scale, anticoagulation, and ICH volume. To our knowledge, this is the first study to demonstrate an association of RDW with mortality in ICH patients, even though two other recent smaller studies provided uncontrolled evidence that RDW may be associated with hematoma expansion within 24 h [13, 14]. The fact that in our study, RDW was not independently associated with long-term mortality after 30 days, would suggest that it could be a marker of the severity of the initial event itself. However, even though higher RDW values were associated with increased neurologic impairment severity as measured by GCS and with increasing ICH scores, there was no correlation between RDW and ICH volume or perihematomal edema volume. We cannot exclude the possibility that RDW may be associated with other neurological and non-neurological acute life-threatening complications after ICH, and information on causes of death was not systematically available. Population-based studies have found that higher RDW values are associated with occurrence of fatal coronary events [15], of incident venous thromboembolism [16] and death related to cancer [17], but it remains to be demonstrated if they contribute to the relationship

| Table 2 Univariable and multivariable binary logistic regression analyses for 30-day mortality (data missing for 2 patients) |
|---------------------------------------------------------------|
| **Univariable analysis** | **Multivariable analysis** |
| **OR (95%CI)** | **p** | **OR (95%CI)** | **p** |
| Age (per 1-year) | 1.03 (1.01–1.05) | 0.003 | 1.01 (0.98–1.03) | 0.691 |
| Male sex | 0.61 (0.38–0.97) | 0.038 | 0.75 (0.36–1.60) | 0.459 |
| Previous functional dependency | 1.65 (0.94–2.89) | 0.082 |
| Previous stroke | 1.20 (0.67–2.16) | 0.537 |
| Arterial hypertension | 1.01 (0.53–1.92) | 0.972 |
| Dyslipidemia | 0.97 (0.60–1.55) | 0.887 |
| Diabetes mellitus | 1.22 (0.71–2.10) | 0.464 |
| Active malignancy | 1.93 (0.53–6.98) | 0.319 |
| Atrial fibrillation | 1.27 (0.69–2.34) | 0.445 |
| Antplatelet therapy | 1.09 (0.65–1.84) | 0.745 |
| Anticoagulation | 1.41 (0.78–2.56) | 0.258 |
| Glasgow Coma Scale (per 1-point) | 0.72 (0.66–0.78) | <0.001 | 0.78 (0.69–0.88) | <0.001 |
| Systolic blood pressure (per 1 mmHg) | 1.00 (1.00–1.01) | 0.353 |
| Diastolic blood pressure (per 1 mmHg) | 1.01 (1.00–1.02) | 0.216 |
| Blood glucose (per 10 mg/dl) | 1.07 (1.03–1.11) | 0.001 | 1.05 (0.99–1.11) | 0.125 |
| Hemoglobin (per 1 g/dl) | 0.80 (0.70–0.92) | 0.002 | 0.99 (0.79–1.24) | 0.908 |
| Neutrophil/lymphocyte ratio | 1.04 (1.00–1.08) | 0.033 | 0.99 (0.93–1.05) | 0.632 |
| Platelet count (per 1 \( \times 10^3/\mu L \)) | 1.00 (1.00–1.00) | 0.900 |
| International normalized ratio (per 1 point) | 1.46 (1.11–1.92) | 0.008 | 1.53 (1.05–2.23) | 0.027 |
| C reactive protein (per 1 mg/dl) | 1.01 (1.00–1.02) | 0.103 |
| RDW-Q4 (vs Q1-Q3) | 1.60 (1.30–1.97) | <0.001 | 3.36 (1.48–7.62) | 0.004 |
| Infratentorial ICH | 1.57 (0.83–2.97) | 0.170 |
| Intraventricular hemorrhage | 3.40 (2.07–5.57) | <0.001 | 1.37 (0.67–2.80) | 0.384 |
| ICH volume (per 1 mL) | 1.03 (1.02–1.04) | <0.001 | 1.03 (1.01–1.05) | <0.001 |
| Perihematomal edema volume (per 1 mL) | 1.03 (1.02–1.04) | <0.001 | 1.00 (0.98–1.02) | 0.883 |
| Perihematomal edema/ICH volume ratio | 0.97 (0.79–1.19) | 0.778 |
| Early infection | 1.34 (0.74–2.42) | 0.332 |
| Baseline ICH score (per 1 point) | 2.86 (2.24–3.65) | <0.001 |

ICH: intracerebral hemorrhage. OR: odds ratio. 95% CI: 95% confidence interval. RDW Q1-4: red cell distribution width quartiles
between RDW and mortality in this population of ICH patients. We also did not find an association between RDW and functional outcome at 3 months. Even though some of the well-known predictors of mortality after ICH are also predictors of functional outcome in ICH survivors [2], RDW appears not to be sensitive to short-term functional outcome. Another hypothesis for explaining this lack of association is a survivorship bias in the groups with lower RDW values, in which a higher short-term survival would consequently be associated with a relative increase in patients with more severe deficits, thus balancing the deleterious effect of RDW on functional outcome.

In accordance with the current literature, atrial fibrillation [18] and active malignancy [17] were more frequent in the groups with higher RDW values, and although they were not predictors of mortality, we cannot exclude a partial contribution to the higher mortality in higher RDW quartile groups. Another possible bias was that groups with higher RDW values were more frequently anticoagulated at baseline, which significantly increases early mortality and hematoma growth, but the predictive role of RDW was also independent of baseline INR. Likewise, the multivariable analysis for 30-day mortality included hemoglobin as a covariate, which reduces the potential bias of anemia as a relevant contributor for increased mortality.

The exact mechanisms explaining why RDW is an anemia-independent predictor of mortality for so many different pathologies, including ischemic stroke [9], subarachnoid hemorrhage [10], acute myocardial infarction [7], atrial fibrillation [18], heart failure [8], acute and chronic renal failure [19, 20], idiopathic pulmonary hypertension [21], acute pancreatitis [22], septic shock [23], cancer [24], and out-of-hospital cardiac arrest [25], remain elusive. Possible pathophysiologic mechanisms such as the association of higher RDW with reduced erythrocyte deformability and consequent microcirculation flow impairment, with nutritional deficits and with chronic systemic inflammation, and oxidative stress, have been listed by several authors [6]. A consistent and robust association of RDW with age and disease burden has been found in several studies [26], and Patel and collaborators have proposed that increasing RDW may, in fact, reflect impairment of multiple physiologic systems related to the aging process [27]. It has been suggested that increased levels of erythropoietin with aging may represent a compensatory mechanism for subclinical blood loss, decreased red blood cell lifespan, and an increased erythropoietin resistance of red cell precursors [28]. Another mechanism which could explain the association of increased RDW with senescence is reduced red blood cell survival due to excessive oxidative stress, known to occur in conditions with accelerated aging such as Down syndrome [29]. In our study, we also found that age was significantly correlated with RDW. This strong correlation and collinearity raises the question of the relative contribution of age and RDW for mortality, which may be difficult to discern [9].

The positive correlation between RDW and CRP in the absence of an association between RDW and early infection, suggests that RDW may indeed be a marker of baseline chronic inflammation. A possible link between RDW, chronic inflammation, and mortality in patients with ICH is the growth of perihematomal edema during the first days after ICH, which is known to be associated with mortality after ICH [30]. A small study in patients with ICH in whom serial magnetic resonance imaging was performed, found a delayed peak perihematomal edema volume in patients with increased hematocrit, but RDW was not reported [31]. Although we did not find an association of baseline RDW with baseline perihematomal edema, further studies should investigate whether higher RDW is associated with increased perihematomal edema growth, which is a potential therapeutic target [32].

The main limitations of our study are related to its retrospective nature, exclusion of 18% of ICH patients because of unavailable CT images for analysis, absent systematic follow-up CT for evaluation of hematoma and edema growth, and absent systematic long-term follow-up for all patients. Information on the causes of deaths was not available for our study, but could provide further understanding of the relationship between RDW and mortality. The main strengths include the fact that the study mirrors a real-life clinical setting, comprehensive clinical, laboratory and imaging characterization of the study population, relatively few missing baseline and follow-up data for the study population, and adjustment of the analyses for the more significant predictors of mortality in ICH patients.

In conclusion, RDW is a robust and independent predictor of 30-day mortality in patients with spontaneous ICH, but does not independently predict long-term mortality. Additional studies to understand the relationship of RDW with early mortality in this population of patients are warranted.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s12028-020-01103-1) contains supplementary material, which is available to authorized users.

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