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ORIGINAL WORK (CLINICAL INVESTIGATION, BASIC SCIENCE)

Association Between Perihematomal Perfusion and Intracerebral Hemorrhage Outcome

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Abstract

Background: The prognostic impact of perihematomal hypoperfusion in patients with acute intracerebral hemorrhage (ICH) remains unclear. We tested the hypothesis that perihematomal hypoperfusion predicts poor ICH outcome and explored whether hematoma growth (HG) is the pathophysiological mechanism behind this association.

Methods: A prospectively collected single-center cohort of consecutive ICH patients undergoing computed tomography perfusion on admission was analyzed. Cerebral blood flow (pCBF) was measured in the manually outlined perihematomal low-density area. pCBF was categorized into normal (40–55 mL/100 g/min), low (< 40 mL/100 g/min), and high (> 55 mL/100 g/min). HG was calculated as total volume increase from baseline to follow-up CT. A modified Rankin scale > 2 at three months was the outcome of interest. The association between cerebral perfusion and outcome was investigated with logistic regression, and potential mediators of this relationship were explored with mediation analysis.

Results: A total of 155 subjects were included, of whom 55 (35.5%) had poor outcome. The rates of normal pCBF, low pCBF, and high pCBF were 17.4%, 68.4%, and 14.2%, respectively. After adjustment for confounders and keeping subjects with normal pCBF as reference, the risk of poor outcome was increased in patients with pCBF < 40 mL/100 g/min (odds ratio 6.11, 95% confidence interval 1.09–34.35, $p = 0.040$). HG was inversely correlated with pCBF ($R = -0.292$, $p < 0.001$) and mediated part of the association between pCBF and outcome (proportion mediated: 82%, $p = 0.014$).

Conclusion: Reduced pCBF is associated with poor ICH outcome in patients with mild-moderate severity. HG appears a plausible biological mediator but does not fully account for this association, and other mechanisms might be involved.

Keywords: Intracerebral hemorrhage, Cerebral blood flow, CT perfusion, Outcome, Stroke

Introduction

Intracerebral hemorrhage (ICH) accounts for up to 50% of stroke-related mortality, and most of the survivors are left with severe disability [1]. Reduced perfusion in the perihematomal region during the acute phase has been frequently reported and may contribute to secondary brain damage, but comprehensive and conclusive studies on its prognostic significance are lacking [2, 3]. However, an association between perihematomal hypoperfusion and hematoma expansion, a known predictor of poor outcome, has been recently reported [4]. In addition, although there is no evidence suggesting the presence of ischemic penumbra in the perihemorrhagic rim [5, 6], the natural history of perihematomal tissue remains controversial. In this regard, a magnetic resonance imaging-based study showed that perihematomal cytotoxic edema in the subacute phase of ICH is not uncommon and

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correlates with unfavorable prognosis [7]. The aim of this computed tomography perfusion (CTP) study was to test the hypothesis that perihematomal hypoperfusion correlates with unfavorable outcome and explore whether hematoma growth (HG) is the pathophysiological mechanism underlying this association.

Methods

The Institutional Review Board of the Azienda Ospedaliera Universitaria, Arcispedale S. Anna, Ferrara, Italy, approved this study. Informed consent was obtained from each patient or close relatives.

Study Population

This was a single-center prospective observational cohort study enrolling consecutive subjects with primary spontaneous ICH [3]. Inclusion criteria were as follows: (1) supratentorial ICH diagnosed within 24 h of onset, (2) baseline and follow-up non-contrast CT (NCCT) images availability, and (3) age > 18 years. Patients with any of the following conditions were excluded: (1) the presence of any intracranial lesion (neoplastic, vascular, or other) presumed or demonstrated to be the ICH source, (2) surgical evacuation of the hemorrhage before follow-up NCCT, (3) pregnancy and lactation, and (4) any other contraindication to the administration of iodinated contrast material.

Clinical Variables

The following variables were collected: demographic data, history of hypertension, antiplatelet or anticoagulant, admission systolic blood pressure (SBP) and diastolic blood pressure (DBP), National Institutes of Health Stroke Scale, time from symptom onset to baseline NCCT, and pre-stroke modified Rankin scale (mRS) [8]. The mRS at three months from the index event was the main outcome of interest and was assessed with telephone interview by trained investigators blinded to clinical and imaging data [9]. Blood pressure target was same for all patients, and blood pressure was managed according to the American Heart Association/American Stroke Association guidelines [10]. Mean arterial pressure was determined with the following formula: DBP + 0.412*(SBP-DBP) [11]. All patients with warfarin-associated coagulopathy received coagulopathy reversal according to the American Heart Association/American Stroke Association [11]. None required platelet transfusions.

Image Acquisition, Processing, and Analysis

All images were acquired on a 64-slice Lightspeed VCT scanner (GE Healthcare, Waukesha, WI, USA). ICH location (deep vs lobar), volume (ABC/2 method), and the presence of intraventricular bleeding were evaluated on baseline NCCT (5-mm slice thickness). Follow-up NCCT was obtained at 24 ± 6 h or earlier in case of clinical deterioration. Hematoma volume was calculated on baseline and follow-up NCCT scans using the formula AxBxC/2 where A, B, and C represent the dimensions of CT hyperdensity in 3 axes perpendicular to each other [12]. Inter-rater reliability between two raters (AM, EF) for ICH volume determination with ABC/2 was calculated with the intraclass correlation coefficient (ICC) on a subgroup of patients ($n = 30$) [13]. The volume of hematoma plus that of perihematomal low-density area was determined according to the same method. Perihematomal edema volume was measured by subtracting the hematoma volume from the combined hematoma and perihematomal low-density area volumes. Borders between perihematomal edema and the subcortical white matter were identified by using windowing and the simultaneous evaluation of averaged CTP images in which the different density between the two tissues was more pronounced. To optimize the identification of perihematomal region boundaries and quantification of its volume, a density threshold was also applied, ranging from 5 to 33 Hounsfield units [14].

ICH growth was calculated as total parenchymal volume increase from baseline to follow-up NCCT variable [15]. CTP studies were performed with a dynamic first-pass bolus-tracking methodology following a one-phase imaging protocol, and cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT) maps were generated using a commercially available delay-sensitive deconvolution software, as previously described [3]. CBF, CBV, and MTT values were measured within a region of interest larger than 1 cm^2 including perihematomal low-density area and drawn freehand on averaged CTP images on every section in which the hematoma was visible (illustrative example in Fig. 1) [3]. Therefore, in each patient, perihematomal CBF, CBV, and MTT levels obtained from each section were averaged. The resulting mean CBF, CBV, and MTT values from all patients were further averaged to generate a single value for perihematomal low-density area. CBF, CBV, and MTT values were measured in mL/100 g/min, mL/100 g and seconds, respectively. Perihematomal perfusion values were expressed as continuous variables and as categorical variables, according to previously proposed thresholds [3]. In particular, CBF was categorized into normal (40–55 mL/100 g/min), low (< 40 mL/100 g/min), and high (> 55 mL/100 g/min), CBV was dichotomized into low (≤ 2.5 mL/100 g) and normal (> 2.5 mL/100 g), and MTT was dichotomized into normal (≤ 5 s) and high (> 5 s).

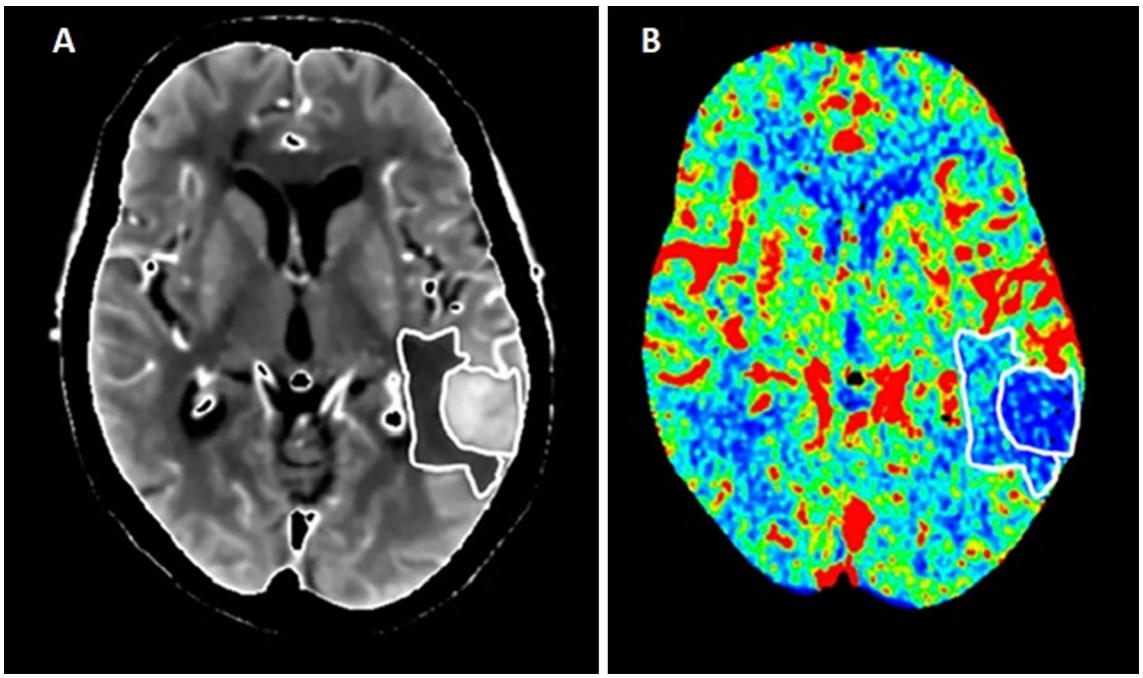

Fig. 1 CT perfusion acquisition. Hematoma topography on averaged computed tomography perfusion images (panel A) and perihematomal perfusion mapping with cerebral blood flow (panel B) in a patient with acute spontaneous intracerebral hemorrhage located in left temporal lobe

Statistical Analysis

Continuous variables were summarized as median (interquartile range, IQR) or mean (standard deviation, SD) based on their distribution (tested with Kolmogorov–Smirnoff test) and compared with Mann–Whitney/Kruskal–Wallis or *t* test/ANOVA as appropriate. Categorical variables were summarized as count (percentage) and compared using the χ^2 test. Unadjusted correlations were evaluated with Spearman test. Partial correlation was used to explore correlations between log-transformed continuous variables after controlling for confounders. Predictors of poor functional outcome, defined as mRS > 2 at three months from the index event [16], were investigated with multivariable logistic regression. Models 1 and 2 were adjusted for the modified ICH score [17], a validated tool to predict poor outcome after ICH, and for HG. In a secondary analysis, the logistic regression models included also all variables with $p < 0.1$ in univariate analyses comparing patients with good and poor outcomes and patients with normal perihematomal CBF, low perihematomal CBF, and high perihematomal CBF. We also performed an additional analysis defining poor functional outcome as mRS > 3 at three months [18].

CBF, CBV, and MTT values in the perihematomal area were analyzed both as continuous variables and as categorical variables in all logistic regression models, to account for the possibility of a non-homogeneous relationship with outcome across different strata [19]. Covariates already incorporated in the modified ICH score were not entered into the logistic regression model. Mediation analysis was performed with R software version 3.2.3. All the other analyses were performed with SPSS 21.0 (www.spss.com), and $p < 0.05$ values were considered statistically significant.

Results

A total of 155 subjects were included (median ICH volume 12.3 mL, interquartile range 5.4–18.2), of whom 55 (35.5%) had poor outcome. The inter-rater reliability for ICH volume determination with ABC/2 was excellent (ICC 0.97, 95% confidence interval 0.94–0.98).

Perihematomal CBF was lower and MTT was higher in patients with unfavorable prognosis, as shown in Table 1. Subjects with poor prognosis had also larger ICH volume and higher values of perihematomal edema and HG. Table 2 describes the study population characteristics stratified by CBF levels. All patients had a baseline pre-stroke mRS ≤ 2 (mRS = 0 in 114 patients, mRS = 1 in 34 patients, mRS = 2 in the remaining 7 patients). Table 3 summarizes the results of multivariable logistic regression. When perihematomal CBF and MTT were analyzed as continuous variables, there was no association with ICH outcome (model 1). However, when CBF was categorized into low ($n = 106$, 68.4%), normal ($n = 27$, 17.4%),

Table 1 Comparison between patients with good versus poor functional outcome

	mRS 0–2 ($n=100$)	mRS 3–6 ($n=55$)	p
Age, median (IQR), *y*	69 (61–75)	68 (64–72)	0.685
Males, *n* (%)	46 (46.0)	27 (49.1)	0.712
Pre-stroke mRS, median (IQR)	0 (0–1)	0 (0–1)	0.635
Hypertension, *n* (%)	58 (58.0)	36 (65.5)	0.363
Antiplatelet treatment, *n* (%)	29 (29.0)	14 (25.5)	0.637
Anticoagulant treatment, *n* (%)	2 (2.0)	5 (9.1)	0.042
SBP, mean (SD), mmHg	153 (29)	150 (27)	0.579
DBP, mean(SD), mmHg	86 (13)	82 (15)	0.055
MAP, mean (SD), mmHg	114 (18)	110 (18)	0.227
NIHSS, median (IQR)	11 (8–14)	20 (18–24)	< 0.001
Time from onset to NCCT, median (IQR) *h*	2.5 (2.2–3.4)	3.1 (2.2–3.5)	0.615
Time from baseline to follow-up NCCT, median (IQR), *h*	17.1 (11.5–19.1)	17.4 (12.1–19.3)	0.656
ICH volume, median (IQR), mL	7.7 (3.9–13.6)	20.9 (13.5–49.3)	< 0.001
Hematoma growth, median (IQR), mL	1.4 (0.8–2.7)	4.9 (2.6–10.0)	< 0.001
ICH location, deep, *n* (%)	63 (63.0)	33 (60.0)	0.713
Intraventricular hemorrhage, *n* (%)	17 (17.0)	20 (36.4)	0.007
Perihematomal edema, median (IQR) mL	17.5 (9.1–27.3)	25 (20–56)	< 0.001
mICH score, median (IQR)	1 (0–1)	2 (2–3)	< 0.001
pCBF, median (IQR), mL/100 g/min	33 (24–48)	29 (17–38)	0.021
pCBV, median (IQR), mL/100 g	2.2 (1.6–3.0)	1.9 (1.4–2.8)	0.149
pMTT, median (IQR), *s*	5.1 (4.3–6.3)	5.7 (4.7–6.9)	0.006

DBP diastolic blood pressure, *ICH* intracerebral hemorrhage, *IQR* interquartile range, *MAP* mean arterial pressure, *mICH score* modified intracerebral hemorrhage score, *mRS* modified Rankin scale, *NCCT* non-contrast computed tomography, *NIHSS* National Institute of Health Stroke Scale, *pCBF* perihematomal cerebral blood flow, *pCBV* perihematomal cerebral blood volume, *pMTT* perihematomal mean transit time, *SBP* systolic blood pressure, *SD* standard deviation

and high ($n=22$, 14.2%), patients with low CBF had a significantly increased risk of poor prognosis when compared to subjects with normal CBF (model 2). This association remained significant also after adjustment for all variables with $p<0.1$ in univariate analyses. We also confirmed the negative prognostic impact of low perihematomal CBF when poor functional outcome was defined as mRS > 3 at 90 days from the index event (odds ratio 7.08, 95% confidence interval 1.70–29.43, $p=0.007$).

Unadjusted analysis showed an inverse correlation between CBF and HG ($R=-0.387$, $p<0.001$) and between CBF and perihematomal edema ($R=-0.288$, $p<0.001$). However, after adjustment for ICH volume, CBF remained independently associated with HG ($R=-0.292$, $p<0.001$), whereas the correlation between CBF and perihematomal edema was no longer significant ($R=0.051$, $p=0.532$). Mediation analysis showed that 82% (95% confidence interval = 40–100%) of the observed effect of perihematomal CBF on outcome could be accounted for by HG (mediation $p=0.014$). This result remained significant after adjustment for the modified ICH score. We further explored the association between perihematomal perfusion, HG, and outcome stratifying perihematomal CBF into the following levels as previously defined [3]: ischemia (< 10 mL/100 g/min), penumbra (10–19 mL/100 g/min), oligemia (20–39 mL/100 g/min), normal (40–55 mL/100 g/min), and hyperperfusion (> 55). Subjects with pCBF values consistent with ischemia had the highest degree of HG (median 22 mL) and the highest frequency of poor outcome (80%), as summarized in Table 4.

Discussion

The association between low perihematomal CBF and unfavorable ICH prognosis is the main finding of our study. This relationship was not linear, and only the presence of CBF < 40 mL/100 g/min was independently associated with higher odds of poor outcome, whereas CBF did not have a prognostic impact when expressed as a continuous variable. This interesting observation may be the consequence of an association between CBF and outcome that is not consistent and uniform across CBF strata, being therefore evident in logistic regression only when CBF is analyzed as a categorical variable, with normal CBF as the reference category [20]. In line with this hypothesis, the frequency of poor outcome across multiple CBF strata followed inverse J-shaped relationship, with the rate of poor prognosis being highest in patients

Table 2 Cohort characteristics stratified by pCBF levels

	All ($n=155$)	Normal pCBF ($n=27$)	Low pCBF ($n=106$)	High pCBF ($n=22$)	p
Age, median (IQR), *y*	68 (61–74)	70 (61–75)	68 (61–74)	68 (61–72)	0.657
Sex, male, *n* (%)	73 (47.1)	14 (51.9)	51 (48.1)	8 (36.4)	0.520
Pre-stroke mRS, median, (IQR)	0 (0–1)	0 (0–1)	0 (0–0)	0 (0–1)	0.606
Hypertension, *n* (%)	94 (60.6)	13 (48.1)	64 (60.4)	17 (77.3)	0.115
Antiplatelet treatment, *n* (%)	43 (27.7)	8 (29.6)	29 (27.4)	6 (27.3)	0.971
Anticoagulant treatment, *n* (%)	7 (4.5)	2 (7.4)	5 (4.7)	0 (0.0)	0.455
SBP, mean (SD), mmHg	152 (28)	142 (21)	154 (29)	154 (29)	0.099
DBP, mean (SD), mmHg	85 (14)	82 (12)	85 (14)	88 (15)	0.331
MAP, mean (SD), mmHg	112 (18)	106 (14)	113 (19)	115 (19)	0.148
NIHSS, median (IQR)	14 (10–19)	11 (8–17)	14 (10–19)	14 (10–20)	0.396
Time from onset to NCCT, median (IQR), *h*	3.0 (2.2–3.5)	3.1 (2.3–3.5)	2.9 (2.2–3.4)	2.8 (2.4–3.6)	0.707
Time from baseline to follow-up NCCT, median (IQR), *h*	17.2 (11.8–19.2)	17.4 (14.1–19–.2	12.9 (9.3–18.5)	18.2 (10.6–19.4)	0.075
Baseline ICH volume, mL	12.3 (5.4–18.2)	4.0 (2.7–18.2)	13.0 (7.3–19.3)	12.1 (6.1–17.3)	0.067
Hematoma growth, median (IQR), mL	2.2 (1.1–4.9)	1.1 (0.5–2.3)	2.4 (1.2–5.5)	2.5 (1.1–4.4)	0.019
ICH location, deep, *n* (%)	96 (61.9)	19 (70.4)	63 (59.4)	14 (63.6)	0.570
Intraventricular Hemorrhage, *n* (%)	37 (23.9)	7 (25.9)	27 (25.5)	3 (13.6)	0.477
Perihematoma edema, mL	20.2 (10.5–32.0)	17 (6–21)	21.7 (13.1–33.7)	14.3 (9.7–27.9)	0.062
mICH score, median (IQR)	1 (1–2)	1 (0–2)	1 (1–2)	1 (1–2)	0.684
mRS > 2 at 90 days, *n* (%)	55 (35.5)	6 (22.2)	42 (39.6)	7 (31.8)	0.224

DBP diastolic blood pressure, *ICH* intracerebral hemorrhage, *IQR* interquartile range, *MAP* mean arterial pressure, *mICH score* modified intracerebral hemorrhage score, *mRS* modified Rankin scale, *NCCT* non-contrast computed tomography, *NIHSS* National Institute of Health Stroke Scale, *pCBF* perihematomal cerebral blood flow, *SBP* systolic blood pressure, *SD* standard deviation

Table 3 Predictors of poor functional outcome (mRS 3–6 at 90 days)

	OR (95% CI)	p
MODEL 1		
mICH score	3.87 (2.24–6.67)	< 0.001
pCBF (mL/100 g/min)	1.00 (0.98–1.03)	0.872
pMTT (s)	1.22 (0.87–1.70)	0.258
Hematoma growth (mL)	1.16 (1.02–1.31)	0.028
MODEL 2		
mICH score	4.42 (2.50–7.83)	< 0.001
pCBF		
Normal (40–55 mL/100 g/min)	Reference	
Low (< 40 mL/100 g/min)	6.11 (1.09–34.35)	0.040
High (> 55 mL/100 g/min)	4.98 (0.72–34.36)	0.103
pMTT, high (> 5 s)	1.06 (0.37–3.01)	0.920
Hematoma Growth (mL)	1.16 (1.02–1.31)	0.025

mICH score modified intracerebral hemorrhage score, *pCBF* perihematomal cerebral blood flow, *pMTT* perihematomal mean transit time

with CBF < 10 mL/100 g/min and increased in patients with high CBF when compared to subjects with normal CBF. In agreement with our study, a previous analysis measuring perihematomal CBF with xenon computed tomography found an increased risk of poor functional outcome at discharge in ICH patients with reduced CBF in the perihemorrhagic rim [2].

Different biological mechanisms may explain our findings. We have recently showed that perihematomal hypoperfusion predicts hematoma expansion [4], and therefore, it appears plausible that hematoma enlargement is one of the mechanisms linking low CBF with ICH prognosis. Mediation analysis confirmed that HG mediated at least part of the association between perihematomal CBF and poor outcome. However, the inclusion of HG in logistic regression did not eliminate the effect of CBF on outcome. Indeed, perihematomal CBF and HG remained associated with poor outcome, independently from each other, suggesting that other biological mediators may explain the link between low CBF and poor ICH prognosis. Reduced CBF may also lead to poor outcome through edema formation. However, in line with previous reports [21], we did not detect an independent association between perihemorrhagic hypoperfusion and edema volume when controlling for ICH volume. This supports the theory that the hemorrhage's mass effect may cause local microvascular hypoperfusion, which in turn leads to edema formation through failure of ion pumps in the perihemorrhagic area [7, 22]. Mitochondrial dysfunction, enhancement of blood brain barrier damage, exacerbation of

Table 4 ICH growth and proportion of patients with poor outcome stratified by perihematomal CBF levels

	Perihematomal CBF, mL/100 g/min					*p*
	< 10	10–19	20–39	40–55	> 55	
	Ischemia (n = 5)	Penumbra (n = 27)	Oligemia (n = 74)	Normal (n = 27)	Hyperemia (n = 22)	
ICH growth, median (IQR), mL	22 (12–24)	6 (3–9)	2 (1–3)	1 (0–2)	3 (1–4)	< 0.001
mRS > 2 at 90 days, *n* (%)	4 (80.0)	14 (51.9)	24 (32.4)	6 (22.0)	7 (31.8)	0.041

CBF cerebral blood flow, *ICH* intracerebral hemorrhage, *IQR* interquartile range, *mRS* modified Rankin scale

p values for HG and proportion of subjects with poor outcome were obtained with Kruskal–Wallis and χ^2 tests, respectively

secondary neuronal injury and inflammation may also account for the prognostic influence of reduced perihematomal CBF, as well as regional hypometabolism [5]. These findings seem to indicate that other mechanisms than ischemia could connect reduced perihematomal CBF with poor outcome. The demonstration that perihematomal area is characterized by preserved regional autoregulation [23] and no CTP evidence of ischemia [3] are consistent with this hypothesis. However, given the clinical setting of our analysis, we do not have data to support or confute these speculations [24–26]. Finally, subjects with a severe reduction of blood flow in the perihemorrhagic area may be more prone to reperfusion damage once the acute phase has resolved [27]. Of note, CBF and not CBV was associated with poor outcome. This could be justified by previous evidence that CBF is more accurate than CBV in the identification of critically hypoperfused tissue [28, 29] and in predicting outcome in patients with acute ischemic stroke [30]. If prospectively confirmed on a larger sample size, our findings may have important implications for clinical practice and future clinical trials. Reduced perihematomal perfusion is common in acute ICH, and given its association with outcome, it might represent an appealing therapeutic target. In addition, accurate estimation of ICH outcome remains an unmet need [31] and the incorporation of CTP parameters may improve the currently available prognostic tools.

Our findings are best interpreted as hypothesis generating, keeping in mind some limitations. Because of the relatively small sample size, we were underpowered to compare multiple CBF categories (ischemia vs penumbra vs oligemia vs normal vs high) in logistic regression. The lack of consensus on the optimal CTP acquisition parameters may limit the generalizability of our results. Furthermore, CTP images were acquired on admission, and therefore, we cannot provide data on perihematomal perfusion in the first hours after symptom onset. Likewise, we were able to account only for admission SBP and this may influenced our results as SBP reduction and its variability in the first 24 h may influence ICH growth [32].

Our findings derive from a non-randomized study, raising the possibility of unmeasured confounders and highlighting the need for external replication. Whether reduced CBF remains associated with poor outcome independently from other imaging predictors remains to be determined [33].

ICH volume quantification with ABC/2 may be less accurate compared to planimetric techniques. This may have influenced our findings as ICH volume is a key predictor of poor prognosis and HG one of the outcomes of interest of our analyses. However, previous studies showed that these two methods seems equivalent in bleedings with limited size [34–36]. Furthermore, a large meta-analysis found that predictors of ICH growth are not influenced by the ICH volume quantification method [37]. The relatively small volumes and an overall mild-to-moderate clinical severity of our study population reduce the generalizability of our findings and suggest the need for confirmation also in more severely affected patients.

Finally, the association between CBF and outcome does not necessarily imply causality and reduced perfusion may simply represent an epiphenomenon of altered metabolic demand in the perihemorrhagic rim [5, 6].

Conclusion

Reduced CBF in the area surrounding the ICH is associated with unfavorable prognosis. HG appears a plausible pathophysiological mediator but does not completely account for the CBF–outcome relationship, and other biological mechanisms might be involved.

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Author Contributions
GB, AB, IC, and EF contributed to data acquisition. AM and SM contributed to statistical analysis. AM and EF contributed to manuscript drafting. AM, GB, AB, SM, IC, and EF contributed to critical revision. EF contributed to study supervision.

Source of Support
None.

Compliance with Ethical Standards

Conflict of interest
The authors declare that they have no conflict of interest.

Ethical Approval/Informed Consent
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The Institutional Review Board of the Azienda Ospedaliera Universitaria, Arcispedale S. Anna, Ferrara, Italy, approved this study. Informed consent was obtained from each patient or close relatives.

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