Delayed Perihematomal Hypoperfusion is associated with

Poor Outcome in Intracerebral Hemorrhage

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ABSTRACT

Background: we aimed to characterize the temporal evolution and prognostic significance of perihematomal perfusion in acute intracerebral hemorrhage (ICH).

Methods: single center prospective cohort of patients with primary spontaneous ICH receiving computed tomography perfusion (CTP) within 6 h from onset (T0) and at 7 days (T7). Cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT) were measured in the manually outlined perihematomal low-density area. Poor functional prognosis (modified Rankin Scale 3-6) at 90 days was the outcome of interest and predictors were explored with multivariable logistic regression.

Results: a total of 150 patients were studied, of whom 52 (34.7%) had a mRS 3-6 at 90 days. Perihematomal perfusion decreased from T0 to T7 in all patients but the magnitude of CBF and CBV reduction was larger in patients with unfavorable outcome (median CBF change -7.8 *vs.* -6.0 mL/100g/min, p<0.001 and median CBV change -0.5 *vs.* -0.4 mL/100g, p=0.010 respectively). This finding remained significant after adjustment for confounders (odds ratio [OR] for 1mL/100g/min CBF reduction: 1.33, 95% confidence interval [CI] (1.15-1.55), p<0.001; OR for 0.1 mL/100g CBV reduction 1.67, 95% CI 1.18-2.35, p=0.004). The presence of CBF<20 mL/100g/min at T7 was then demonstrated as an independent predictor of poor functional outcome (adjusted OR: 2.45, 95% CI 1.08-5-54, p=0.032).

Conclusion: perihemorrhagic hypoperfusion becomes more severe in the days following acute ICH and is independently associated with poorer outcome. Understanding the underlying biological mechanisms responsible for delayed decrease in perihematomal perfusion is a necessary step towards outcome improvement in patients with ICH.

INTRODUCTION

Intracerebral hemorrhage (ICH) is a life-threatening cerebrovascular event arising from acute bleeding in the brain parenchyma [1]. ICH remains a deadly disorder, with up to 40% early mortality and severe long term disability in the majority of survivors [2]. Despite being less common than ischemic stroke, ICH accounts for more than half of early deaths for acute cerebrovascular events [3]. Accurate stratification of ICH prognosis is therefore a clinical research priority and is highly desired also in the setting of randomized controlled trials [4]. However, the diagnostic performance of most of the currently available prognostic prediction tools remains suboptimal and precise prediction of ICH outcome remains an unmet need [3].

Hypoperfusion of the perihemorrhagic area has been reported in ICH and may be associated with poor functional outcome [5]. However, most of the evidence so far available is limited to the hyperacute phase using baseline perfusion imaging obtained on admission [5,6]. Temporal evolution and clinical significance of perihematomal perfusion evolution during the subacute phase remains underinvestigated. Preliminary studies suggested that perihemorrhagic hypoperfusion may persist beyond the acute phase but these findings derive from studies with non-consecutive small sample size using different imaging modalities [7,8]. Furthermore, the prognostic impact of longitudinal cerebral perfusion change remains unknown.

The aim of this study was to explore the temporal evolution of perihemorrhagic perfusion over time and assess its relationship with ICH functional outcome.

METHODS

Patient enrollment and assessment

The is an analysis of a single center prospective observational cohort enrolling consecutive subjects with primary spontaneous ICH from January 2010 to July 2016 [9]. This study was specifically designed to explore the longitudinal evolution of cerebral perfusion in patients with acute ICH and included patients meeting the following inclusion criteria: I) diagnosis of supratentorial ICH within 6 h of onset, II) age > 18 years III) pre-stroke modified Rankin Scale (mRS) < 2 and IV) availability of baseline (admission, T0) and follow-up (day 7, T7) CT perfusion (CTP). We excluded subjects with any of the following conditions: I) ICH secondary to

neoplastic, vascular or other brain lesion, II) anticoagulant treatment with vitamin K antagonists and international normalized ratio > 1.5 or treatment with direct oral anticoagulants or other known coagulopathy, III) surgical treatment and IV) absolute contraindication to the administration of iodinated contrast material.

Age, sex, hypertension, antiplatelet treatment, admission blood pressure (BP), stroke severity (according to national institute of health stroke scale[NIHSS]), time from onset to baseline non-contrast CT (NCCT), and modified Rankin Scale (mRS) at 90 days from the index event were collected.

Medical management and in particular blood pressure lowering followed the American Heart Association / American Stroke Association guidelines [10,11].

Clinical variables were acquired with direct interview to patients or relatives or from available medical records whereas mRS was assessed by telephone interview by trained investigators, blinded to all clinical and imaging data.

The Institutional Review Board approved all the procedures of this study. Data are available upon reasonable request to the Corresponding Author. The investigation conforms with the principles outlined in the Declaration of Helsinki, and all participants provided written informed consent to participate in the study.

Image Acquisition, Processing and Analysis

All images were acquired on a 64-slice Lightspeed VCT scanner (GE Healthcare, Waukesha, WI, USA) and baseline NCCT were analyzed for determination of ICH ~~location (deep vs lobar)~~, volume (semi-automated, computer-assisted planimetric measurement with the software ITK-SNAP 3.8.0)[12] and presence of intraventricular hemorrhage. ICH location was defined as lobar (bleeding in cortex and cortical-subcortical junction) versus deep (bleeding involving the thalamus, basal ganglia, internal capsule or deep periventricular white matter)[13] .

All patients underwent a follow-up NCCT at 24 hours, or sooner in case of clinical deterioration. Perihematomal edema volume was measured on NCCT by subtracting the hematoma volume from the combined hematoma and perihematomal low density area volumes.

CTP perfusion was obtained on admission, within 6 hours from symptom onset (T0) and at 7 days (T7) from the index event. We used a CTP dynamic first-pass bolus-tracking methodology following a one-phase imaging protocol and cerebral blood flow (CBF, mL/100g/min), cerebral

blood volume (CBV, mL/100g) and mean-transit-time (MTT, seconds) maps were generated using a commercially available delay-sensitive deconvolution software. [9] Perfusion values were measured within a region of interest larger than 1 cm^2 including the perihematomal low-density area and drawn freehand on averaged CTP images in every section with evidence of bleeding. [9] An illustrative example is provided in Figure 1. Perihemorrhagic perfusion parameters were analyzed as absolute values and as dichotomic variables, using the following cutoffs: CBF< 20 mL/100g/min, CBV< 2.5 ml/100g and MTT >5 s [9]. We also analyzed the absolute change in these parameters from baseline T0 to T7 (ΔCBF, ΔCBV, ΔMTT). All the images were analyzed by a neuroradiologist with more than 10-year experience in CTP acquisition and interpretation.

Endpoint adjudication and power calculation.

The primary outcome of the study was to test whether CPT perfusion was able to independently predict poor functional prognosis, defined by a mRS 3-6 at three month after primary spontaneous ICH. Our statistical power to detect a 20% difference in the rate of poor outcome between patients with normal versus low perihematomal perfusion, assuming a type I error rate (alpha) of 0.05, was greater than 70%.

Statistical Analysis

Continuous variables are expressed as median and interquartile range [IQR] as the normality assumption was not demonstrated. Unpaired intergroup comparisons were drawn by Mann-Whitney U-test. Categorical variables were expressed as count (percentage) and compared using the χ^2 test. The primary outcome was explored with multivariable logistic regression. All logistic regression models were adjusted for the modified ICH score [14] and for perihematomal edema [15]. In a secondary analysis, the logistic regression model was adjusted for baseline ICH volume [16]. Finally we also performed an analysis accounting for ICH expansion, defined as hematoma growth >33% and/or >6 mL. All the analyses were performed with IBM SPSS Statistics for Windows, Version 21.0 (IBM CO., Armonk, NY). For all statistical analyses a 2-sided p-value <0.05 was considered as statistically significant.

Reporting of the study conforms to broad EQUATOR guidelines [17].

RESULTS

A total of 223 patients with ICH were screened during the study period. After exclusion of 73 subjects (41 with secondary ICH or coagulopathy, 19 unable to complete the imaging protocol or

with poor quality images, 7 requiring surgical treatment and 6 unable to receive iodinated contrast) the remaining 150 patients were included, of whom 52 (34.7%) had poor functional outcome. Table 1 summarizes general characteristics of the study population.

Unpaired group comparisons between patients with good *vs.* poor functional outcome are shown in Table 2 and in Figure 2. CBF values were similar across the two study groups at T0 whereas at T7 subjects with poor functional outcome had significantly lower CBF (19.1 *vs.* 26.6 mL/100g/min, P=0.012) and a higher proportion of patients with CBF<20 mL/100g/min (61.5% vs 32.7%, P=0.001).

Patients with unfavorable prognosis had a significantly larger CBF and CBV reduction from admission to day 7 (ΔCBF -7.8 vs -6.0 mL/100g/min, P <0.001 and ΔCBV -0.5 vs -0.4 mL/100g, P =0.010 respectively), as shown in Figure 2.

When included in adjusted logistic regression models, none of the CTP parameters at T7 – analyzed as continuous variables – were independently associated with poor functional outcome, as summarized in Figure 3. Conversely, ΔCBF and ΔCBV were demonstrated as independent predictors of poor functional outcome after adjustment for confounders. In particular, each mL/100g/min of CBF reduction was associated with a 33% increase in the odds of poor prognosis (odds ratio (OR) 1.33, 95% confidence interval (CI) 1.15-1.55 P <0.001). The same finding was observed for CBV, with every 0.1 mL/100g of CBF reduction increasing the odds off poor functional outcome by 67% (OR 1.67, 95% CI 1.18-2.35, P=0.004). When perfusion values at T7 were dichotomized, only low the presence of CBF<20 mL/100g/min predicted poor prognosis (OR 2.45, 95% CI 1.08-5-54, P=0.032).

In secondary analyses adjusting for baseline ICH volume, CBF and CBV reduction remained independently associated with functional outcome independently from ICH size (OR for ΔCBF 1.30, 95% CI 1.14-1.49, P<0.001 and OR for ΔCBV 1.51, 95% CI 1.13-2.01, P=0.005)

All these findings were confirmed also after adjustment for ICH expansion in logistic regression.

DISCUSSION

In the present study we observed that perihemorrhagic hypoperfusion in patients with ICH persists and becomes more severe in the days following the hyperacute phase, and is associated with poorer functional outcome. We failed to identify an independent prognostic impact of absolute

perfusion values at T7 but rather the magnitude of CBF and CBV reduction from baseline to follow-up CTP had a negative impact on functional outcome.

Several biological mechanisms may explain our findings. First, perihematomal perfusion may be an epiphenomenon of perihematomal edema formation [15,18] and the longitudinal evolution of perfusion values might possibly represent an indirect consequence of edema evolution. However, this hypothesis is not substantiated by our findings as there was no correlation between perfusion and edema extent at 7 days. In addition, the prognostic impact of hypoperfusion remained significant at logistic regression analysis also when adjusted for edema. Another more plausible explanation is the development of secondary irreversible ischemic damage due to compression and thrombotic events in ICH adjacent vessels. Previous MRI studies indirectly support this hypothesis [19,20]. Although there is solid evidence suggesting that cerebral autoregulation is preserved in the acute phase of ICH, [21] these mechanisms may be unable to fully compensate for large reductions in perihematomal perfusion occurring days after the bleeding onset, leading therefore to ischemic parenchymal damage. In agreement with this hypothesis, we observed that the degree of CBF and CBV drop was associated with poor functional outcome whereas absolute perfusion values at one week were not. Other studies did not confirm the presence of perihemorrhagic penumbra, [22] but this discrepancy may be explained by the small sample size with a minority of patients receiving a perfusion study beyond 5 days from onset. Furthermore, recent data have shown a significant association between perihematomal hypoperfusion and irregular hemorrhage shapes, [23] and while this may seem unrelated, previous evidence suggests that irregularity of hemorrhage borders on baseline CT may be an indirect biomarker of both hemorrhage immaturity (that is, with either persisting bleeding or unsettled peripheral mass effect) and poorer outcome [24]. Similarly, the present study provides additional evidence that perihematomal hypoperfusion and its evolution over time may be an important biomarker of ICH formation and evolution pathophysiological mechanisms.

Our findings are best interpreted as hypothesis generating and may have important implications for future research studies. ICH remains a devastating disorder, with limited therapeutic targets and effective treatments that are strongly time-dependent [10,11]. Conversely, perihematomal hypoperfusion develops over days and is independently associated with poor functional outcome. Perihematomal hypoperfusion therefore presents opportunities to better understand the pathophysiological mechanisms leading to worse outcomes, beyond the initial parenchymal damage. Pending replication and future studies aimed at identifying patients at higher risk of

developing delayed perihematomal hypoperfusion, this biomarker may be a first step towards the development of novel therapeutic strategies, targeted at the perihematomal environment.

Some limitations should be considered in the interpretation of our results. First, selection bias in favor of less severely affected patients may have occurred, as only patients able to complete the CTP protocol at one week were included. Second, variations in BP and cerebral perfusion pressure over time may have influenced our results and we were not able to properly account for these potential confounders and in particular for BP outside the acute phase. Furthermore, patients were collected over a relatively long time frame and during the study period different ICH guidelines were published with relevant discrepancies in BP targets in the acute ICH phase [10,11]. Third, we did not have validation data with a different imaging modality (i.e. magnetic resonance imaging) and therefore we cannot rule out the presence of confounding factors related to the imaging technique and specifically to CTP [25]. Fourth, CT angiography was not part of our standard imaging protocol in ICH and therefore we cannot exclude the presence of vascular stenoses which, considering the use of a delay-sensitive software in our analysis, could promote delay and dispersion of the contrast bolus resulting in underestimation of CBF values[25-27]. However, as previously recommended[25], we selected the arterial inputfunction (AIF)in an artery of contralateral unaffected hemisphere to minimize the inaccuracyin the quantification of CTP parameters.

Finally, the presence of an association between hypoperfusion and poor prognosis does not necessarily imply a causal link and more studies are needed to confirm our findings and characterize the underlying pathophysiological mechanisms.

In conclusion, perihemorrhagic hypoperfusion at one week from onset is common, and independently associated with outcome in patients with ICH. Understanding the biological mechanisms responsible for delayed decrease in perihematomal perfusion is a necessary step towards outcome improvement in patients with ICH, to explore therapeutic strategies targeted at the perihematomal environment.

Conflict of Interest:

Andrea Morotti reports no disclosures;
Giorgio Busto reports no disclosures;

Gregoire Boulouis reports no disclosures;

Elisa Scola reports no disclosures;

Andrea Bernardoni reports no disclosures;

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Enrico Fainardi reports no disclosures.

Authors Contribution:

Andrea Morotti: Study concept and design, data analysis and interpretation. Statistical Analysis. Manuscript drafting and critical revision

Giorgio Busto: Data acquisition, analysis and interpretation. Critical revision.

Gregoire Boulouis: Data acquisition, analysis and interpretation. Critical revision.

Elisa Scola: Data acquisition, analysis and interpretation. Critical revision.

Andrea Bernardoni: Data acquisition, analysis and interpretation. Critical revision.

Alessandro Fiorenza: Data acquisition, analysis and interpretation. Critical revision.

Tommaso Amadori: Data acquisition, analysis and interpretation. Critical revision.

Federico Carbone: Data analysis and interpretation. Critical revision.

Ilaria Casetta: Data acquisition, analysis and interpretation. Critical revision.

Fabrizio Montecucco: Data analysis and interpretation. Critical revision.

Enrico Fainardi: Manuscript drafting. Data acquisition, analysis and interpretation. Critical revision. Study Supervision.

Ethical Approval:

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. All the study aspects were approved by the Ethical Committee of the L'Azienda Ospedaliero-Universitaria di Ferrara "Arcispedale Sant'Anna", Via Aldo Moro, 8, 44124 Ferrara (FE), Italy.

Informed Consent:

Informed consent was obtained from all individual participants included in the study.

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Table 1. Clinical and radiological features of the overall cohort (n=150).

Age, [IQR], years	68 [61-74]
Sex, male, n (%)	71 (47.3)
History of hypertension, n (%)	92 (61.3)
Antiplatelet treatment, n (%)	42 (28.0)
SBP, [IQR], mmHg	150 [130-170]
DBP, [IQR], mmHg	80 [80-91]
NIHSS, [IQR]	14 [10-19]
Time from onset to NCCT, [IQR] hours	3.1 [2.4-3.8]
Baseline ICH volume, mL	12 [6-19]
Follow-up ICH volume, mL	16 [7-25]
ICH location, deep, n (%)	91 (60.7)
Presence of IVH, n (%)	37 (24.7)
T0 Perihematomal edema, mL	20 [11-32]
T7 Perihematomal edema, mL	28 [16-53]
mICH score, [IQR]	1 [1-2]
T0 CBF, [IQR], mL/100g/min	30.9 [21.0-47.6]
T7 CBF, [IQR], mL/100g/min	24.2 [17.3-40.3]
T0 CBV, [IQR], mL/100g	2.0 [1.3-3.0]
T7 CBV, [IQR], mL/100g	1.7 [1.0-2.6]
T0 MTT, [IQR], s	5.2 [4.5-6.6]
T7 MTT, [IQR], s	5.6 [4.9-7.0]
mRS 3-6 at three months, n (%)	52 (34.7)

Data are presented as median [IQR] or absolute and relative (%) frequencies.

ICH: intracerebral hemorrhage; SBP: systolic blood pressure; DBP: diastolic blood pressure; NIHSS: national institute of health stroke scale; NCCT: non-contrast computed tomography; IVH: intraventricular hemorrhage; CBF: cerebral blood flow; CBV: cerebral blood volume; mRS: modified Rankin Scale.

Table 2. Comparison between subjects with poor and good functional outcome.

	90 days mRS 0-2	90 days mRS 3-6	P -value
	(n=98)	(n=52)	
Age, [IQR], y	69 [61.74]	68 [64-72]	0.734
Sex, male, n (%)	47 (48.0)	24 (46.2)	0.833
History of hypertension , n (%)	59 (60.2)	33 (63.5)	0.697
Antiplatelet treatment, n (%)	27 (27.6)	15 (28.8)	0.866
SBP, [IQR], mmHg	150 [130-170]	150 [130-178]	0.878
DBP, [IQR], mmHg	80 [80-95]	80 [70-90]	0.112
NIHSS, [IQR]	11 [8-14]	20 [18-24]	<0.001
Baseline ICH volume, mL	10 [4-14]	19 [13-47]	<0.001
Follow-up ICH volume, mL	12 [6-18]	26 [16-65]	<0.001
ICH expansion, n (%)	32 (32.7%)	22 [42.3%]	0.241
ICH location, deep, n (%)	60 (61.2)	31 (59.6)	0.848
Presence of IVH, n (%)	19 (19.4)	18 (34.6)	0.039
mICH score, [IQR]	1 [0-2]	2 (2-3)	<0.001
T0 Perihematomal edema, mL	18 [10-28]	23 [19-56]	<0.001
T7 Perihematomal edema, mL	22 [13-36]	44 [30-87]	<0.001

Data are presented as median [IQR] or absolute and relative (%) frequencies. Comparisons were drawn by Mann-Whitney U-test or $\chi 2$ test, as appropriate.

ICH: intracerebral hemorrhage; SBP: systolic blood pressure; DBP: diastolic blood pressure; NIHSS: national institute of health stroke scale; NCCT: non-contrast computed tomography; IVH: intraventricular hemorrhage; CBF: cerebral blood flow; CBV: cerebral blood volume; mRS: modified Rankin Scale.

FIGURE LEGEND

Figure 1. CT perfusion acquisition.

Perihematomal perfusion mapping performed at admission (Panel A) and at 7 days (Panel B) after baseline scans on averaged computed tomography perfusion images (Averaged CTP), and cerebral blood flow (CBF), cerebral blood volume (CBV) and mean transit time (MTT) maps in a patient with acute spontaneous intracerebral hemorrhage located in the left parietal lobe.
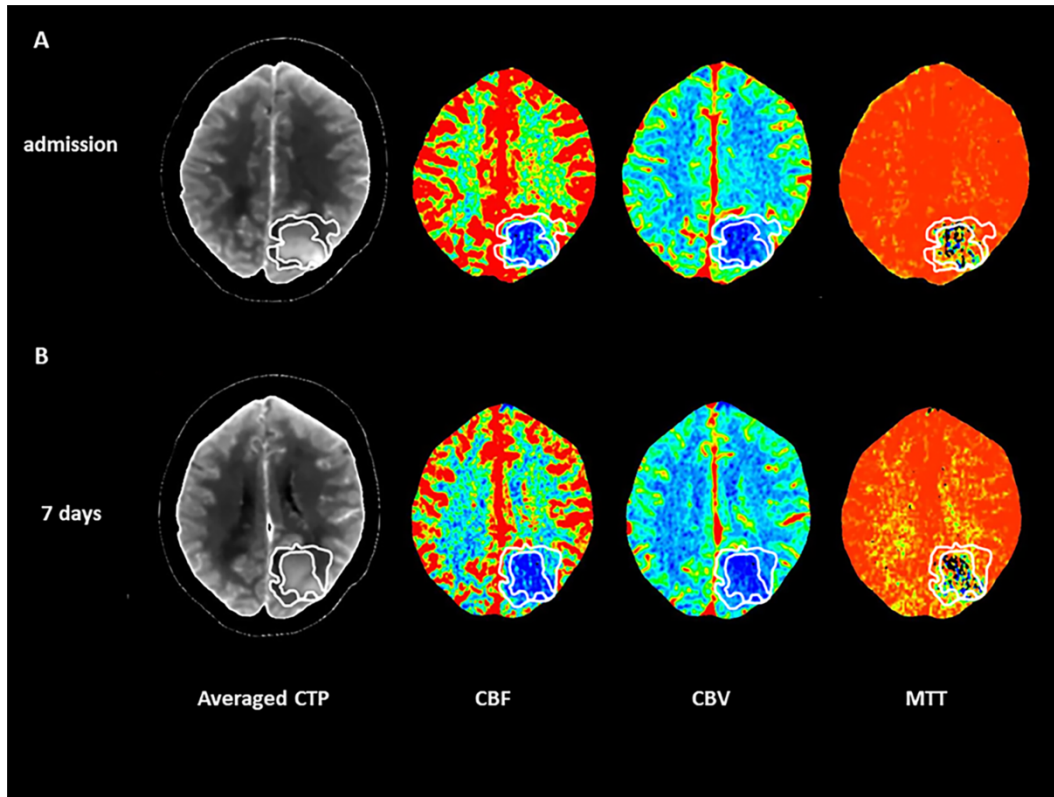
Figure 2. Perihematomal perfusion on admission and day 7

T0 indicates day 0 (admission); T7 indicates day 7; pCBF, perihematomal cerebral blood flow; pCBV, perihematomal cerebral blood volume; pMTT, perihematomal mean transit time; mRS, modified Rankin Scale.
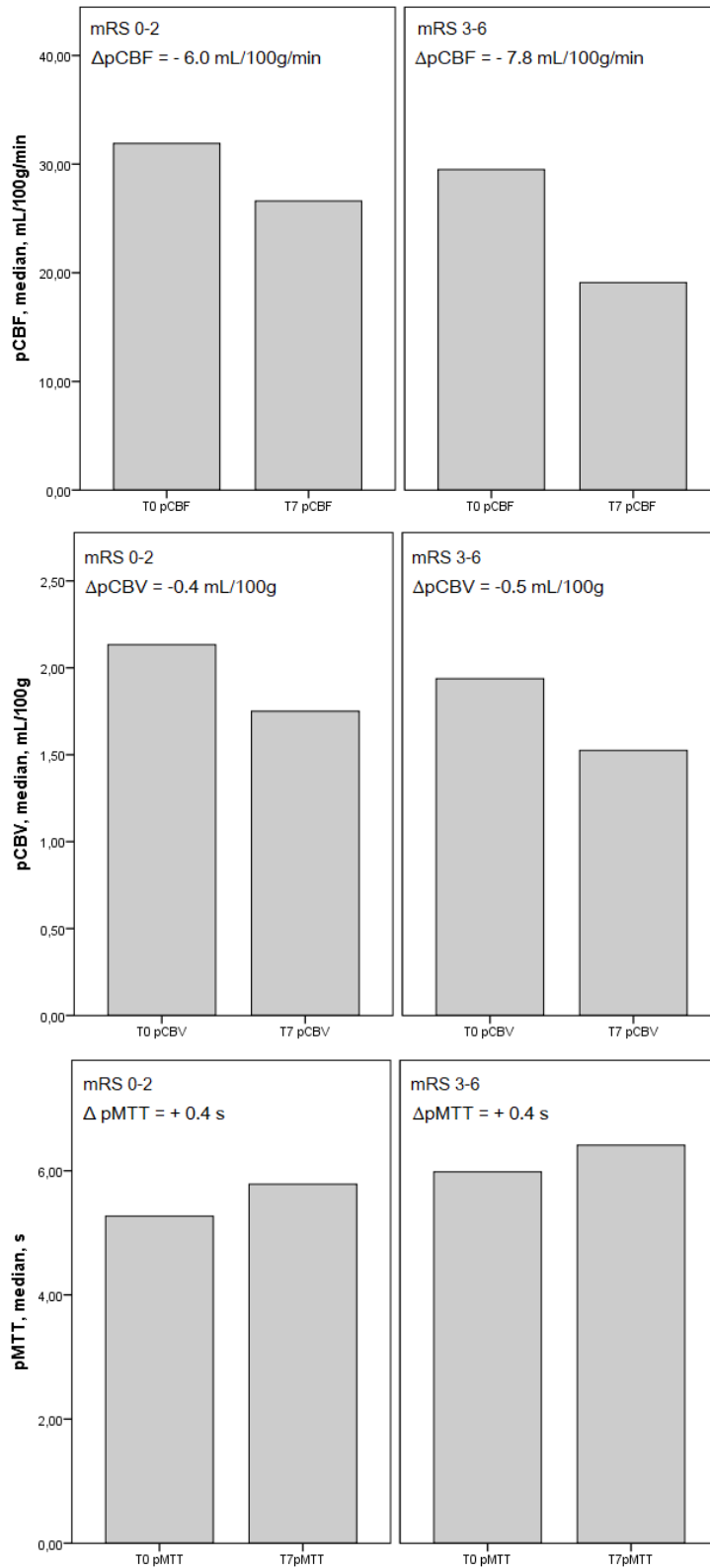
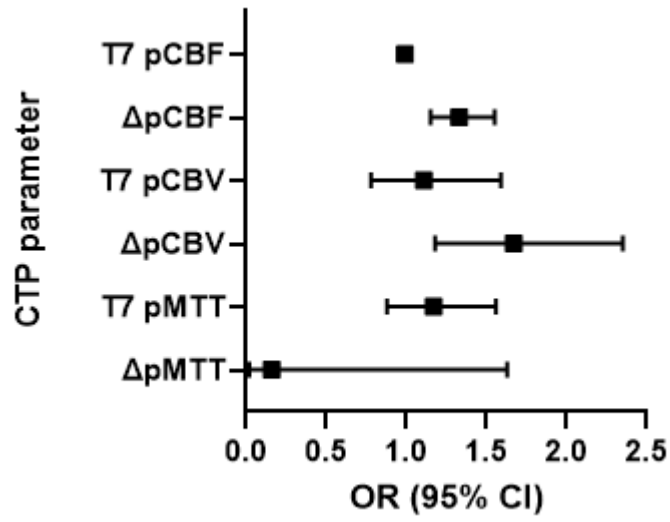**Figure 3.** Predictors of poor functional outcome

OR indicates odds ratio; 95% confidence interval; pCBF, perihematomal cerebral blood flow; pCBV, perihematomal cerebral blood volume; pMTT, perihematomal mean transit time; mRS, modified Rankin Scale.

Poor functional prognosis, defined as mRS 3-6 at 90 days from the index event, was the outcome of interest. Independent predictors of poor functional outcome were explored with multivariable logistic regression, accounting for the modified ICH score and perihematomal edema volume. The results of multivariable logistic regression are presented as OR (95% CI).

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